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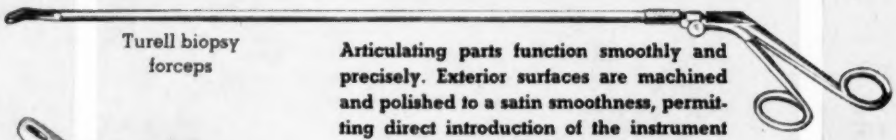

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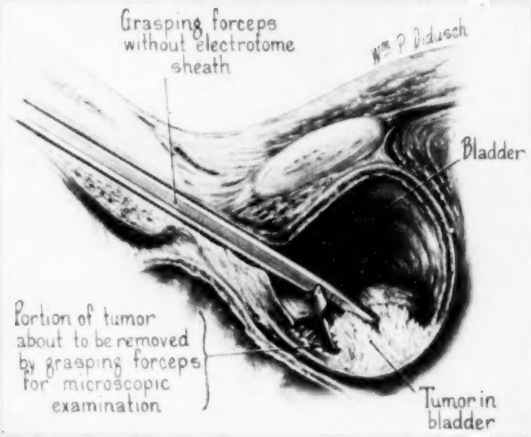
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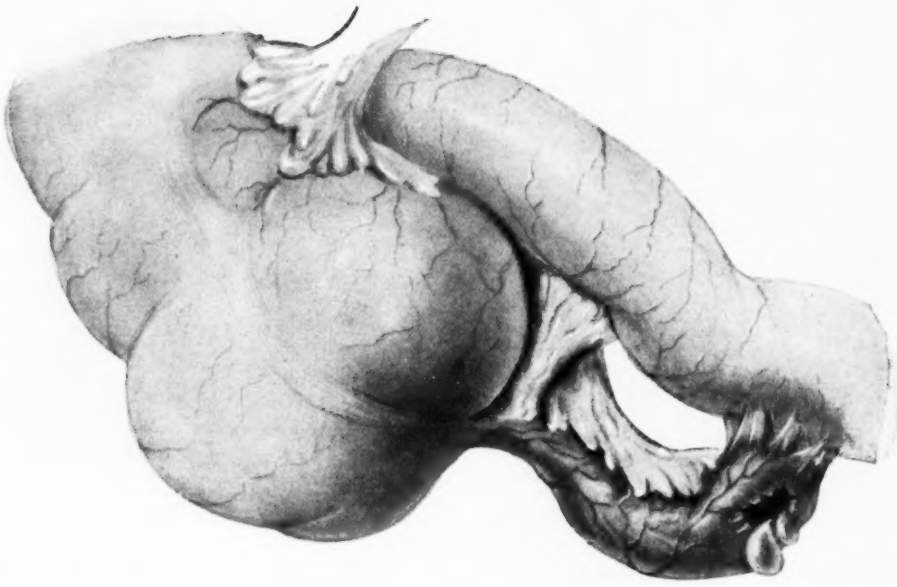

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*Schaeffer, J. R., and Pulaski, E. J.: U. S. Armed Forces M. J. 1:1447 (Dec.) 1950.*

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VOLUME 64 JUNE 1952 NUMBER 6

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# ALBUMIN AND GLOBULIN CHANGES IN BURNS AS DEMONSTRATED BY ELECTROPHORESIS

JOHN J. PRENDERGAST, M.D.
RICHARD L. FENICHEL, M.S.
AND
BYRNE M. DALY, M.D.
DETROIT

HERETOFORE there has been no report of a systematic electrophoretic study of a series of human burn patients. Shedlovsky and Scudder [1] described an increase in the alpha globulin fraction of a single patient suffering from first, second and third degree burns. Murakami [2] studied the chemolytic albumin-globulin ratios of four patients who had suffered first and second degree burns and found that the globulin portion was somewhat increased at the expense of the albumin portion.

In the present investigation, blood protein patterns for a series of burn patients have been studied at regular intervals from the onset of thermal injury, through the period of the body's response to this stress, and until the onset of healing. Altogether, blood serum and blood plasma of eight hospitalized patients suffering primarily second and third degree burns ranging in extent from 10 to 35% of the total surface area of the body have been surveyed.

## EXPERIMENTAL TECHNIQUE

Between 40 and 50 ml. of blood was drawn from each burn patient at regular time intervals. About half the amount of blood was permitted to clot, and as the clot retracted the clear serum was separated and centrifuged. The remainder of the blood sample in each case was placed in a tube containing calcium oxalate, and the plasma was separated from the red cells.

After the serum and plasma had been clarified by centrifugation, 5 ml. of each was mixed with 10 ml. of barbital buffer at pH 8.6 and ionic strength of 0.1. They were then placed in separate bags of "Visking" tubing and each dialyzed against 1 liter of buffer for 24 hours at refrigerator temperature.

Studies were performed with the Aminco-Stern electrophoresis apparatus in accordance with the standard technique previously reported.[3] Total protein values for both serum and plasma were determined by standard Kjeldahl analysis, and from these data the absolute values of the individual protein fractions were computed.

From the Medical Department, Chrysler Corporation.

Mr. Russell Robertson gave technical assistance during this investigation.

Dr. Osborne A. Brines, pathologist, and the resident surgeons at Detroit Receiving Hospital cooperated by enabling us to obtain blood samples in burn cases used in this study.

1. Shedlovsky, T., and Scudder, J.: A Comparison of Erythrocyte Sedimentation Rates and Electrophoretic Patterns of Normal and Pathological Human Blood, J. Exper. Med. **75**:119-126, 1942.

2. Murakami, T.: Studies on the Serum Proteins in Burns, Jap. J. Dermat. & Urol. **34**:85, 1933.

3. Reiner, M.; Fenichel, R. L., and Stern, K. G.: Electrophoretic Studies on the Protein Distribution in Normal Human Serum, Acta haemat. **3**:202-210, 1950.

TABLE 1.—*Relative and Absolute Serum Protein Values*

| Patient | Sample | Degree and Area Burned | Total Protein | A/G | Relative Values in % | | | | | Absolute Values in Gm./100 Cc. | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Alb | $\alpha_1$ | $\alpha_2$ | $\beta$ | $\gamma$ | Alb | $\alpha_1$ | $\alpha_2$ | $\beta$ | $\gamma$ |
| Normal Values [a] | ..... | | 7.22 | 1.33 | 56.8 | 7.2 | 8.7 | 12.8 | 14.4 | 4.1 | 0.5 | 0.6 | 0.9 | 1.0 |
| | | 30% | | | | | | | | | | | | |
| R. D. | 12 hr. | 2 & 3 | 7.00 | 0.61 | 38.0 | 6.1 | 12.3 | 21.4 | 22.2 | 2.7 | 0.4 | 0.9 | 1.5 | 1.6 |
| | 4 days | 2 & 3 | 7.18 | 0.49 | 32.7 | 10.3 | 13.1 | 25.0 | 19.0 | 2.4 | 0.7 | 0.9 | 1.8 | 1.4 |
| | 7 days | 2 & 3 | 5.65 | 0.31 | 23.6 | 9.2 | 16.1 | 20.1 | 31.0 | 1.3 | 0.5 | 0.9 | 1.1 | 1.8 |
| | 12 days | 2 & 3 | 7.01 | 0.22 | 18.8 | 8.5 | 13.9 | 17.3 | 41.5 | 1.3 | 0.6 | 1.0 | 1.2 | 2.9 |
| | 19 days | 2 & 3 | 7.03 | 0.16 | 13.7 | 7.7 | 13.7 | 13.7 | 51.1 | 1.0 | 0.5 | 1.0 | 1.0 | 3.6 |
| | 27 days | 2 & 3 | 6.35 | 0.22 | 17.9 | 8.4 | 17.9 | 12.9 | 42.8 | 1.1 | 0.5 | 1.1 | 0.8 | 2.7 |
| | | 15% | | | | | | | | | | | | |
| D. T. | 4 hr. | 1, 2, & 3 | 7.06 | 0.64 | 39.1 | 8.0 | 11.0 | 16.8 | 25.2 | 2.8 | 0.6 | 0.8 | 1.2 | 1.8 |
| | 24 hr. | 1, 2, & 3 | 6.55 | 0.59 | 37.1 | 8.9 | 14.2 | 14.4 | 25.2 | 2.4 | 0.6 | 0.9 | 0.9 | 1.7 |
| | 2 days | 1, 2, & 3 | 7.15 | 0.46 | 31.6 | 10.2 | 16.1 | 15.7 | 26.4 | 2.3 | 0.7 | 1.2 | 1.1 | 1.9 |
| | 4 days | 1, 2, & 3 | 7.11 | 0.51 | 34.0 | 10.7 | 14.5 | 15.6 | 25.2 | 2.4 | 0.8 | 1.0 | 1.1 | 1.8 |
| | | 35% | | | | | | | | | | | | |
| M. M. | 2 hr. | 2 & 3 | 7.61 | 0.62 | 38.4 | 7.8 | 11.0 | 25.6 | 17.3 | 2.9 | 0.6 | 0.8 | 1.9 | 1.3 |
| | 8 days | 2 & 3 | 5.80 | 0.37 | 27.1 | 15.3 | 16.1 | 17.8 | 23.8 | 1.6 | 0.9 | 0.9 | 1.0 | 1.4 |
| | 11 days | 2 & 3 | 5.72 | 0.34 | 25.4 | 11.8 | 18.8 | 15.9 | 27.2 | 1.5 | 0.7 | 1.1 | 1.0 | 1.6 |
| | 13 days | 2 & 3 | 6.59 | 0.34 | 25.4 | 14.3 | 16.6 | 16.2 | 27.6 | 1.7 | 0.9 | 1.1 | 1.1 | 1.8 |
| | 15 days | 2 & 3 | 5.90 | 0.33 | 24.7 | 14.3 | 17.5 | 18.2 | 25.4 | 1.5 | 0.8 | 1.0 | 1.1 | 1.5 |
| | 20 days | 2 & 3 | 6.77 | 0.26 | 20.8 | 16.4 | 21.3 | 18.0 | 23.6 | 1.4 | 1.1 | 1.4 | 1.2 | 1.6 |
| | 24 days | 2 & 3 | 6.55 | 0.37 | 27.2 | 14.4 | 17.7 | 21.3 | 19.4 | 1.8 | 0.9 | 1.2 | 1.4 | 1.3 |
| | 30 days | 2 & 3 | 7.00 | 0.37 | 27.0 | 14.6 | 16.7 | 21.1 | 20.6 | 1.9 | 1.0 | 1.2 | 1.5 | 1.4 |
| | | 15-18% | | | | | | | | | | | | |
| S. K. | 5 min. | 3 | 7.97 | 0.82 | 45.2 | 7.1 | 12.9 | 19.2 | 15.7 | 3.6 | 0.6 | 1.0 | 1.5 | 1.3 |
| | 12 hr. | 3 | 6.73 | 0.74 | 42.5 | 8.3 | 14.9 | 17.9 | 16.2 | 2.9 | 0.6 | 1.0 | 1.2 | 1.1 |
| | 24 hr. | 3 | 6.45 | 0.59 | 37.4 | 12.4 | 17.7 | 22.2 | 10.5 | 2.4 | 0.8 | 1.1 | 1.4 | 0.7 |
| | 3 days | 3 | 5.80 | 0.41 | 29.3 | 16.0 | 21.0 | 21.8 | 12.0 | 1.7 | 0.9 | 1.2 | 1.3 | 0.7 |
| | 7 days | 3 | 6.98 | 0.29 | 22.2 | 15.4 | 18.2 | 22.6 | 21.6 | 1.6 | 1.1 | 1.3 | 1.6 | 1.5 |
| | 12 days | 3 | 7.50 | 0.34 | 25.1 | 13.7 | 15.8 | 22.1 | 23.4 | 1.9 | 1.0 | 1.2 | 1.7 | 1.8 |
| | 30 days | 3 | 6.65 | 0.38 | 27.8 | 11.3 | 15.9 | 16.7 | 29.2 | 1.9 | 0.8 | 1.0 | 1.1 | 1.9 |
| | | 25% | | | | | | | | | | | | |
| W. N. | 24 hr. | 2 | 6.70 | 1.04 | 51.0 | 8.8 | 10.4 | 15.9 | 13.9 | 3.4 | 0.6 | 0.7 | 1.1 | 0.9 |
| | 48 hr. | 2 | 5.70 | 0.82 | 45.0 | 13.6 | 14.9 | 19.1 | 7.4 | 2.6 | 0.8 | 0.9 | 1.1 | 0.4 |
| | 4 days | 2 | 5.25 | 0.54 | 35.1 | 15.6 | 21.1 | 16.8 | 11.4 | 1.8 | 0.8 | 1.1 | 0.9 | 0.6 |
| | 9 days | 2 | 6.25 | 0.31 | 23.8 | 13.6 | 21.0 | 20.6 | 21.0 | 1.5 | 0.9 | 1.3 | 1.3 | 1.3 |
| | 18 days | 2 | 6.39 | 0.36 | 26.4 | 16.0 | 16.7 | 18.0 | 25.9 | 1.7 | 0.8 | 1.1 | 1.2 | 1.7 |
| | | 25% | | | | | | | | | | | | |
| J. H. | 24 hr. | 2 & 3 | 5.79 | 0.67 | 40.1 | 11.1 | 10.5 | 18.4 | 19.8 | 2.3 | 0.6 | 0.6 | 1.1 | 1.2 |
| | 48 hr. | 2 & 3 | 5.57 | 0.48 | 32.3 | 12.3 | 16.0 | 19.7 | 19.8 | 1.8 | 0.7 | 0.9 | 1.1 | 1.1 |
| | 4 days | 2 & 3 | 7.35 | 0.44 | 30.6 | 13.5 | 19.6 | 18.8 | 17.6 | 2.3 | 1.0 | 1.4 | 1.4 | 1.3 |
| | 8 days | 2 & 3 | 7.16 | 0.37 | 27.2 | 12.8 | 18.3 | 18.8 | 22.9 | 2.0 | 0.9 | 1.3 | 1.4 | 1.6 |
| | 16 days | 2 & 3 | 7.24 | 0.41 | 29.2 | 11.7 | 16.6 | 17.9 | 24.7 | 2.1 | 0.8 | 1.2 | 1.3 | 1.8 |
| | 34 days | 2 & 3 | 5.70 | 0.37 | 27.0 | 13.1 | 20.1 | 18.8 | 21.0 | 1.5 | 0.7 | 1.1 | 1.1 | 1.2 |
| | | 10% | | | | | | | | | | | | |
| R. W. | 12 hr. | 1 & 2 | 5.25 | 0.60 | 37.6 | 11.1 | 14.8 | 21.8 | 14.6 | 2.0 | 0.6 | 0.8 | 1.1 | 0.8 |
| | 48 hr. | 1 & 2 | 5.40 | 0.58 | 36.8 | 13.1 | 13.8 | 20.8 | 15.4 | 2.0 | 0.7 | 0.7 | 1.1 | 0.8 |
| | 4 days | 1 & 2 | 4.85 | 0.46 | 31.3 | 12.5 | 17.8 | 21.0 | 17.5 | 1.5 | 0.6 | 0.9 | 1.0 | 0.9 |
| | 8 days | 1 & 2 | 5.25 | 0.34 | 25.2 | 15.5 | 20.9 | 20.1 | 18.2 | 1.3 | 0.8 | 1.1 | 1.1 | 1.0 |
| | 26 days | 1 & 2 | 5.94 | 0.38 | 27.6 | 14.4 | 16.3 | 20.8 | 21.0 | 1.6 | 0.9 | 1.0 | 1.2 | 1.2 |
| | | 25% | | | | | | | | | | | | |
| G. P. | 15 min. | 2 & 3 | 6.06 | 0.87 | 46.5 | 7.6 | 16.2 | 13.9 | 15.7 | 2.8 | 0.5 | 1.0 | 0.8 | 1.0 |
| | 15 hr. | 2 & 3 | 6.06 | 0.50 | 33.1 | 11.0 | 18.0 | 18.3 | 19.7 | 2.0 | 0.7 | 1.1 | 1.1 | 1.2 |
| | 48 hr. | 2 & 3 | 5.25 | 0.49 | 32.6 | 15.5 | 14.5 | 17.4 | 20.0 | 1.7 | 0.8 | 0.8 | 0.9 | 1.1 |
| | 7 days | 2 & 3 | 5.02 | 0.38 | 27.7 | 16.5 | 19.0 | 16.0 | 20.8 | 1.4 | 0.8 | 1.0 | 0.8 | 1.0 |
| | 15 days | 2 & 3 | 5.40 | 0.26 | 20.5 | 16.0 | 20.5 | 17.0 | 26.0 | 1.1 | 0.9 | 1.1 | 0.9 | 1.4 |
| | 26 days | 2 & 3 | 5.76 | 0.39 | 27.9 | 14.5 | 16.9 | 13.7 | 27.0 | 1.6 | 0.8 | 1.0 | 0.8 | 1.6 |

From each of the eight burn patients, serum and plasma were collected as soon as possible after the burn and then as close to the schedule of 8 hours, 24 hours, 48 hours, 4 days, 8 days, 16 days, and 30 days as could be adhered to.

Since previous studies have shown the effects of age and sex on the electrophoretic spectrum to be negligible, the present investigation ignores these variables.

Most of the patients studied were subject to repeated whole-blood transfusions—8 to 14 such transfusions having been administered during the respective 30-day period following the burn. That these transfusions had relatively little effect on the electrophoretic spectrum is shown in the following results.

## RESULTS

The Table presents both relative and absolute electrophoretic values, including albumin-globulin ratios and total protein concentrations for the serum of each patient studied. Values determined from plasma were substantially the same as

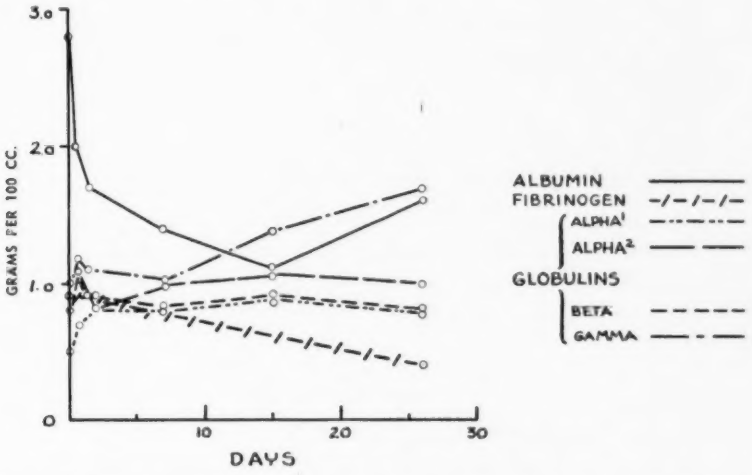


Chart 1.—Patient G. P., with second and third degree burns covering 25% of body surface.

those derived from serum but included fibrinogen measurements not available from the latter.

As may be seen, albumin-globulin ratios show a steady decline in practically every case. Rate of decline is greater for the more serious burn cases—those involving predominantly third degree burns and covering 25 to 35% of the total body surface—and continues until a minimal value is reached when, with the onset of recovery, a gradual rise begins.

Total protein measurements show the substantial loss of serum protein that occurred in these burn cases. Despite repeated whole-blood transfusions, total protein at best remained level and in most cases declined.

Charts 1, 2, and 3 show the variation of absolute serum component values with time for the three burn patients with some second and mainly third degree burns involving 25 to 35% of the total body surface. Albumin shows a sharp drop followed by a more gradual drop until a minimum value is reached and, finally, an indication

of increase. Gamma globulin shows the greatest single increase of all the globulins, and alpha $_2$ globulin shows the next greatest increase. The first 15 to 20 days appear to be the time during which the greatest decrease is recorded for albumin and the greatest increase noted for the gamma and alpha $_2$ globulins.

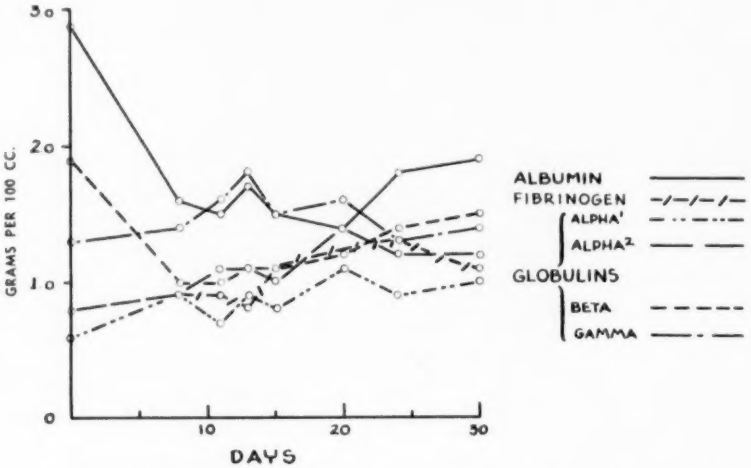


Chart 2.—Patient M. M., with second degree burns covering 35% of body surface.

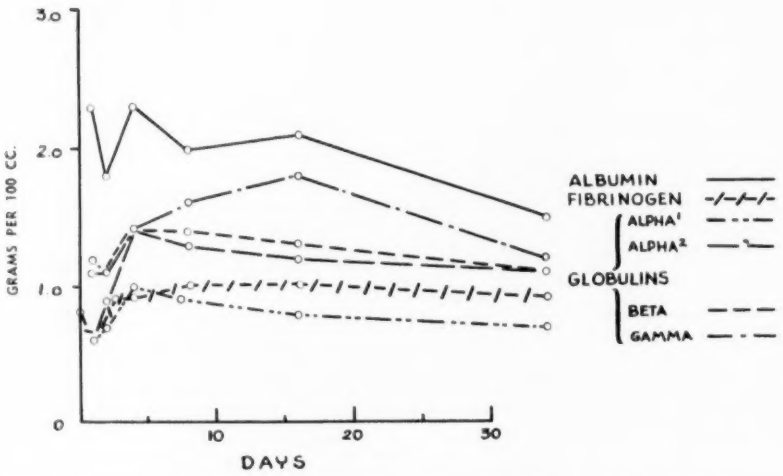


Chart 3.—Patient J. H., with second and third degree burns covering 25% of body surface.

Chart 4 shows the same type plot for a patient, R. D., with serious (30% second and principally third degree) burns. Here we note the albumin decrease as well as the very pronounced gamma-globulin increase. At autopsy, the adrenal gland of R. D. showed hemorrhages.

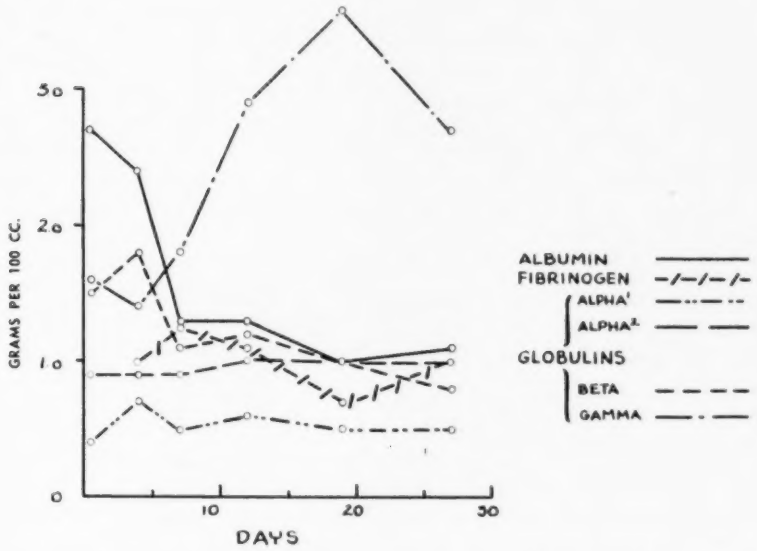


Chart 4.—Patient R. D., with second and third degree burns covering 30% of body surface.

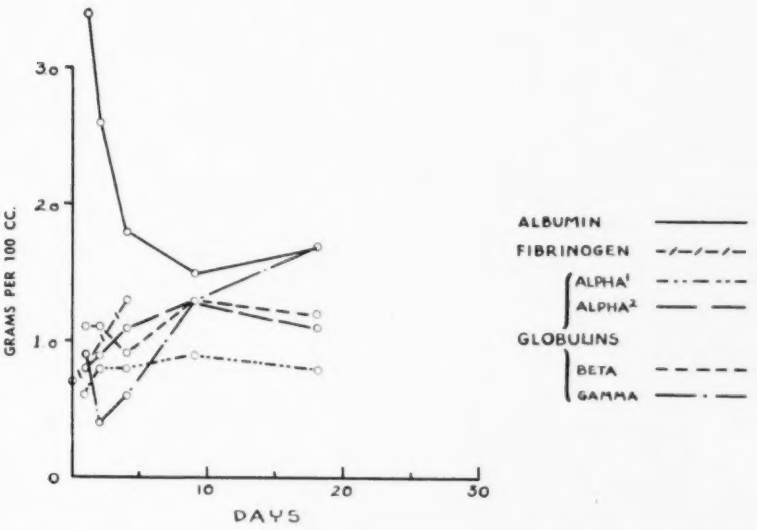


Chart 5.—Patient W. N., with second degree burns covering 25% of body surface.

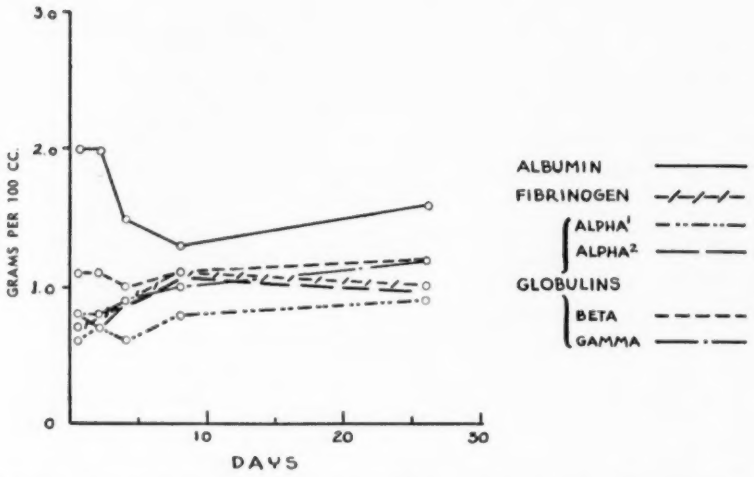


Chart 6.—Patient R. W., with first and second degree burns covering 10% of body surface.

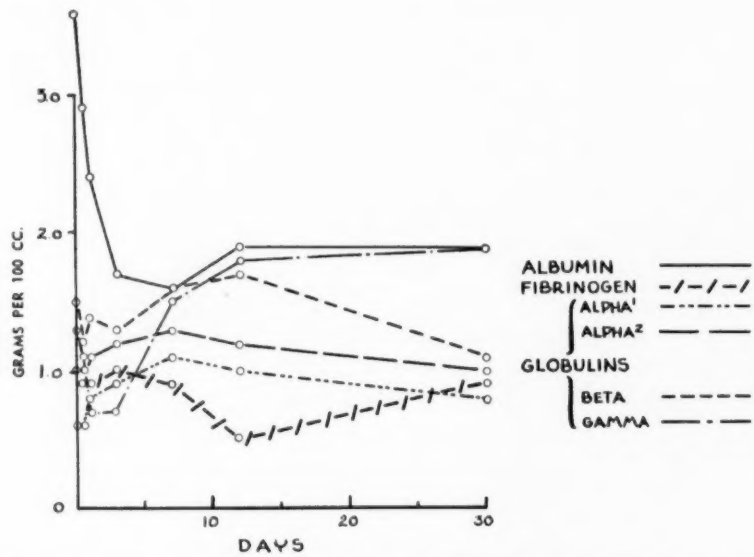


Chart 7.—Patient S. K., with third degree burns covering 15 to 18% of body surface.

In the case of W. N. (Chart 5), a healthy young man with first and second degree burns covering 25% of body surface, we observe the expected albumin decline. Also, after a brief initial decline, the increase in gamma concentration follows the pattern observed in the other severe burn cases studied.

In this case we were able to obtain a sufficient quantity of blister fluid for total protein and electrophoretic analysis. The total protein value was 2.44 gm. per 100 cc., with albumin accounting for 1.0 gm. alpha $_1$ globulin accounting for 0.4 gm. and the alpha $_2$, beta, and gamma globulin fractions accounting for 1.0 gm. of the total.[4] These figures are interesting in that they show the amounts of material lost through the surface of the burn.

Chart 6 shows the changes with time of the albumin, fibrinogen, and globulin fractions of a patient suffering from 10% first and second degree burns. Here, too, we note the sharp initial albumin decrease. In the globulin region, the alpha $_2$ globulin shows the sharpest change. In this case, gamma globulin shows what could be considered a negligible increase.

Chart 7 portrays the case of S. K., a patient with third degree burns covering 15 to 18% of the body surface. Unfortunately, it is not possible to ascertain the effects of the burn in this case because the patient was also suffering from metastatic carcinoma involving the brain, the lungs, and the liver. Whether the burn through systemic stimulation fostered the spread of this cancer and thereby hastened the patient's death is at this time speculative.

## COMMENT

Comparison of serum component values for the more seriously burned patients (Charts 1 to 4) with those of a less seriously burned patient (Chart 6) suggests that gamma globulin is the best indicator of burn severity. All the former patients exhibit a profound increase in gamma-globulin concentration, with the maximum rise occurring in the fatal case (Chart 4). The least seriously burned patient shows but little increase in gamma-globulin concentration.

It is generally accepted that the liver is the site of both albumin and fibrinogen formation. The results obtained and outlined herewith tend to confirm this point. With steady and rapid albumin loss, the liver is called upon to produce albumin. At the same time fibrinogen is also produced because of such stimulation. Albumin, however, because of its small particle size and spherical shape, is readily lost through the burned area. Thus we have the indicated situation of an albumin decrease and a fibrinogen increase.

If albumin were to be added to the system in a relatively pure form (purified normal human serum albumin), it would be expected that stress on the liver would diminish and thereby reduce the fibrinogen level, with resultant improvement in the patient's condition. This rationale is supported by Woodruff and Gibson,[5] who found that, clinically, administration of pure human serum albumin to burn patients replaced lost albumin and prevented or corrected hemoconcentration.

In the fatal case, that of R. D., it would seem that the liver had reached its maximum capacity for overt response and was still not able to compensate for

4. Named concentrations were identified on the basis of electrophoretic mobility.

5. Woodruff, L. M., and Gibson, S. T.: Use of Human Albumin in Military Medicine: The Clinical Evaluation of Human Albumin, U. S. Nav. M. Bull. **40**:791-796, 1942.

albumin loss. Its function was gradually impaired and finally reduced to a negligible degree. At autopsy, the liver of this patient was found to be almost totally necrotic.

Recent experimental work has shown lymphoid structures of the body as important contributors of gamma globulin.[6] Moreover, the work of Perlmann, Glenn, and Kaufman [7] suggests that such lymphoid contributions of gamma globulin may arise in two ways. In addition to direct production of gamma globulin, their investigation indicated that the lymphoid structures also transport gamma-globulin-like material released by cellular destruction of tissue in the burn area. Both of these gamma-globulin fractions are presumed to appear subsequently in the blood serum.

Thus, in the present study, observed increases in gamma globulin may well have resulted in good measure both from stimulation of regular lymphoid gamma production and, also, from the lymph-transported gamma-globulin-like material created in the burn itself.

The alpha $_2$ globulin increase reported in this study of burns may be due to the stimulation of the liver as well as the extrahepatic tissue. Fundamental work of the type conducted by Roberts and White [8] on rat liver slices is necessary before the site of production of this component can be more clearly defined.

## SUMMARY

Results of the first known electrophoretic study of a series of human burn patients (eight) clearly indicate that electrophoresis provides a valuable method of evaluating the severity of burns and the progress of such patients.

Of all the separable components in the electrophoretic spectrum, gamma-globulin concentration appears to provide the best index of burn severity. In relatively minor cases, those involving 10 to 15% of body area and consisting of first and second degree burns, there is little increase in gamma-globulin concentration. In major cases, those involving 25 to 35% of body area and second and third degree burns, there is great increase in gamma-globulin concentration.

Electrophoretic measurements in this study show that whole-blood transfusions, even when frequently repeated, do not correct the abnormal blood picture produced in moderate to serious burns. In view of this fact, it appears that whole-blood transfusion therapy is inadequate.

Evidence available at this time suggests that better therapeutic results might be secured if, in addition to whole blood, burn patients requiring blood replacement therapy were to be transfused with purified normal human serum albumin or a blood substitute suitable for albumin replacement.

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6. White, A., and Dougherty, T.: The Role of Lymphocytes in Normal and Immune Globulin Production and the Mode of Release of Globulin from Lymphocytes, Ann. New York Acad. Sc. **46**:859-882, 1946. Harris, T. N.; Grimm, E.; Mertens, E., and Ehrich, W. S.: The Role of the Lymphocyte in Antibody Formation, J. Exper. Med. **81**:73-83, 1945. Kass, E. H.: The Occurrence of Normal Serum Gamma-Globulin in Human Lymphocytes, Science **101**:337-338, 1945.

7. Perlmann, G. E.; Glenn, W. W. L., and Kaufman, D.: Changes in the Electrophoretic Pattern in Lymph and Serum in Experimental Burns, J. Clin. Invest. **22**:627-632, 1943.

8. Roberts, S., and White, A.: Studies on the Origin of the Serum Proteins, J. Biol. Chem. **180**:505-516, 1949.

# USE OF STREPTOKINASE-STREPTODORNASE (VARIDASE®) TO LYSE CLOTTED BLOOD OBSTRUCTING BILIARY DRAINAGE

## Obstruction Following Cholecystectomy and Choledochotomy

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AND

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NEW YORK

THE OBJECT of this report is to demonstrate a clinical use for the fibrinolytic properties of streptokinase-streptodornase (varidase®) in the dissolution of clotted blood obstructing the postoperative drainage of the common duct following cholecystectomy and choledochotomy.

### REPORT OF A CASE

A 57-year-old white woman was admitted to St. Vincent's Hospital on June 5, 1951, with a chief complaint of epigastric pain, chills, and sore throat of three days' duration.

In the initial interview the patient related that she had had recurrent episodes of upper abdominal pain associated with nausea and vomiting during the past 10 years. These symptoms were occasionally brought on or aggravated by fatty or fried foods. She did not recall having clay-colored stools, dark urine, or jaundice. The relevant past history included the statement that she had had a "malignant breast tumor" 12 years previously for which a radical mastectomy had been performed. Upon admission physical examination revealed that the patient's temperature was elevated to 102.4 F. The pertinent physical findings were limited to the pharynx and abdomen. An acute pharyngitis was present without cervical lymphadenopathy. The abdomen was soft. However, palpation over the right upper quadrant elicited tenderness. No masses were palpable. There was no icterus. A clinical diagnosis of acute pharyngitis and chronic cholecystitis with lithiasis was made.

*Laboratory Data.*—The blood count showed 3,780,000 red cells, 10.5 gm. of hemoglobin, and 9,800 white cells, with a normal differential count. The urine was normal. The Kahn reaction was negative; serum amylase, 78 mg. per 100 cc. Total serum proteins were 7.1 gm. and blood urea nitrogen was 12 mg. per 100 cc. The electrocardiogram and findings on the chest roentgenogram were within normal limits. X-ray examination of the upper intestinal tract with barium revealed no abnormalities. Two attempts with iodoalphionic acid (priodax®) in various concentrations failed to visualize the gall bladder roentgenographically.

Fifteen days after admission the abdomen was explored through a right subcostal incision. A thickened gall bladder was found, containing many small calculi. In addition, the common duct proximal to the duodenum was dilated two or three times the normal size. This duct was opened and a large soft friable calculus was removed. The biliary ducts were irrigated and probed, and a rubber catheter was passed into the duodenum. A T-tube was inserted in the common duct, and a cholecystectomy with drainage concluded the operation.

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The first five days of the patient's postoperative course were uneventful. The T-tube drained 150 to 200 cc. of clear bile each day. On the sixth day blood appeared in the T-tube and bile drainage ceased. An attempt to irrigate the tube with isotonic sodium chloride solution produced severe pain to the patient and a temperature of 105 F. A small amount of clotted blood was recovered from the tube on withdrawal of the solution. A cholangiogram was obtained with use of 35% iodopyracet concentrated solution (diodrast®); dilatation of the midportion of the common duct was demonstrated. No dye was seen in either the duodenum or the hepatic ducts.

The patient became markedly icteric, and the serum bilirubin was elevated to 17. The T-tube was threaded with a No. 18 gauge polyethylene catheter, and a continuous drip (2 drops

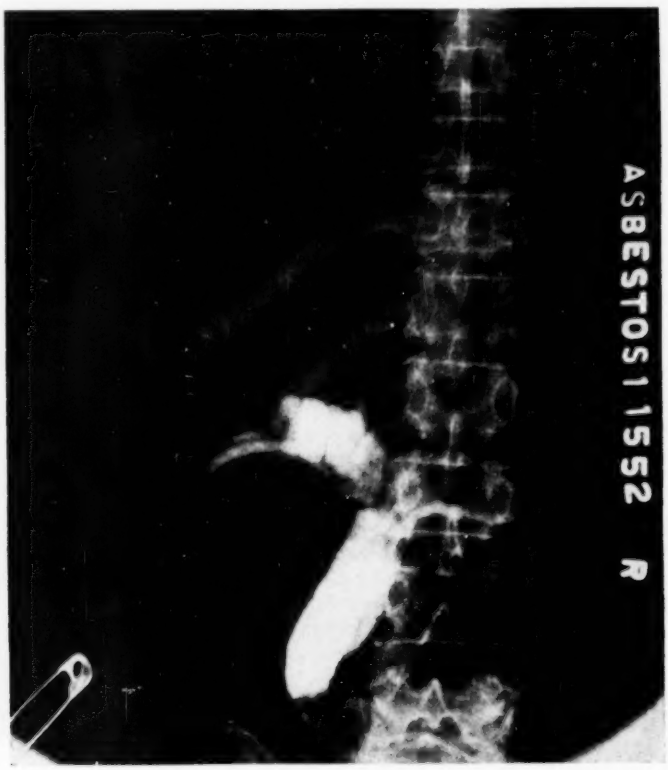


Fig. 1.—Cholangiogram taken June 27, 1951. Note obstructed and dilated common duct, lack of patent pancreatic duct, and nonvisualized hepatic radicles.

per minute) of isotonic sodium chloride solution containing 400,000 units of streptokinase and 100,000 units of streptodornase per liter was started.

At first dark blood-stained fluid returned as drainage about the catheter in the T-tube. The outflow gradually became a lighter hue of red and finally on the third day became bile-stained. By the end of 96 hours the return fluid contained clear bile. This was associated with a lessening of the icterus, a fall in the serum bilirubin, and a sense of well-being on the part of the patient. A cholangiogram repeated six days after the initial film revealed the dye in the duodenum and outlining of the hepatic ducts.

Subsequent investigations of the patient, including an exhaustive hematological study, failed to reveal the cause of the hemorrhage.

The use of the streptococcal fibrinolytic enzymes of lyse clotted blood in vitro and in vivo has been recorded.[1] In our experience we have utilized this property of the enzymes on blood from the patients to determine whether the serum has the necessary substrates or has inhibiting streptofibrinolysin antibodies.

In the report described, the patient's serum contained active substrates; a closed cavity was available, and the material to be lysed was a substrate susceptible to this enzyme system. The closed cavity in this instance was the common bile duct, lined with columnar epithelium, rather than the serous cavities of the thorax and abdomen or the artificial cavities developed for a flat-surface wound. The streptococcal

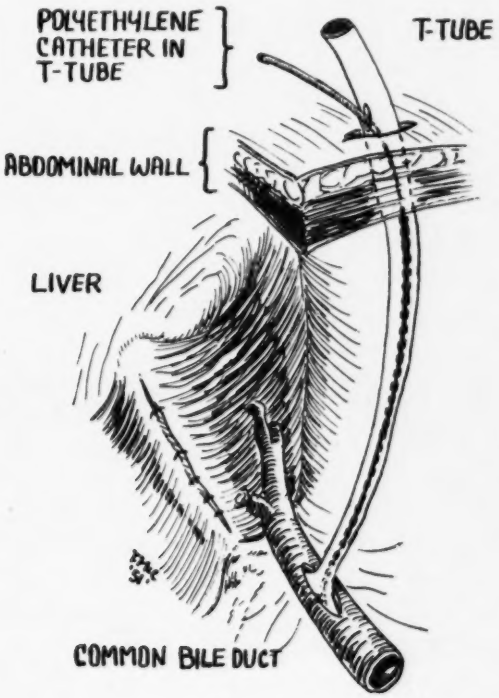


Fig. 2.—Intubation of common duct for continuous perfusion of obstructed lumen with steptokinase-streptodornase (varidase®).

1. Tillet, W. S., and others: Streptococcal Enzymatic Debridement, Ann. Surg. **131**:12, 1950. Tillet, W. S.: Fibrinolytic Activity of Hemolytic Streptococci, Bact. Rev. **2**:161, 1950. Tillet, W. S.; Sherry, S., and Christensen, L. R.: Streptococcal Desoxyribonuclease: Significance in Lysis of Purulent Exudates and Production by Strains of Hemolytic Streptococci, Proc. Soc. Exper. Biol. & Med. **68**:184, 1948. Tillet, W. S., and Sherry, S.: The Effect in Patients of Streptococcal Fibrinolysin and Streptococcal Desoxyribonuclease on Fibrinous Purulent and Sanguinous Pleuralexudations, J. Clin. Invest. **28**:173, 1949. Christensen, L. R.: Methods of Measuring the Activity of Components of the Streptococcal Fibrinolytic System and Streptococcal Desoxyribonuclease, ibid. **28**:163, 1949. Connell, J. F., Jr., and Rousselot, L. M.: The Use of Enzymatic Agents in the Debridement of Burn and Wound Sloughs, Surgery **30**:43, 1951.

fibrinolytic enzymes atraumatically removed the clotted blood from the obstructed external biliary drainage system, thereby obviating a major surgical procedure in a critically ill patient.

We have used the above method to relieve acute urinary retention secondary to blood clots in the bladder following suprapubic prostatectomy. In both instances large-caliber drainage tubes were blocked, but we were able to run in a continuous flow of the enzyme solution. In three to four hours the retention was relieved. For complete evacuation of clots from the bladder, mechanical irrigation was neces-

Fig. 3.—Cholangiogram taken July 3, 1951, showing common duct still dilated after treatment; with obstruction removed so that dye appears in the two hepatic branches and in the duodenum.

sary. It must be remembered in investigating these problems with various enzymes that the physiological criteria particular to each enzyme system, such as pH, specific substrates available, and concentration of active enzyme, must be met and maintained.

## SUMMARY

The successful use of streptokinase-streptodornase to dissolve clotted blood obstructing common duct drainage in a patient after operation is presented. Further uses of this fibrinolytic agent are discussed.

# HOMOLOGOUS TRANSPLANTATION OF THE LUNG

## Preliminary Report of Technical Studies

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HOMOLOGOUS transplantation of tissues and organs has been, on the whole, unsuccessful. Nevertheless, functionally useful homotransplants in man have been obtained with various tissues, such as the cornea,[1] blood vessels,[2] and skin.[3] These results are encouraging to the surgeon, since they suggest that more knowledge of the factors responsible for the destruction of homografts may enable him to apply the technic of homotransplantation to a wide variety of tissues and organs.

The homologous transplantation of an entire lung has not been performed up to the present time either in lower animals or in man. The purpose of this investigation was twofold: (1) to determine whether homologous transplantation of a whole lung is feasible from the viewpoint of surgical technic, and (2) to ascertain the behavior of the transplanted lung with respect to its structure and function.

Considerable difficulties were encountered in performing the operation of homotransplantation of a whole lung. Finally a technic was developed which enabled us to complete the procedure successfully in a number of animals. We believed it desirable to record in this paper for the benefit of others interested in the homotransplantation of tissues our technical procedures and results.

### TECHNIC OF TRANSPLANTATION

Dogs weighing from 30 to 50 lb. (14 to 23 kg.) were used. Intratracheal intubation was performed, and ether-oxygen anesthesia was administered by means of an automatic respirator (Burns valve). In order to develop a uniform technic, we transplanted the same lung (left lung) in each experiment. However, our results would have been equally valid if the right lung had been chosen. The animal was placed in the right lateral position, and the fifth rib was exposed and resected for a distance of 6 to 8 in. (15 to 20 cm.) from the costochondrosternal junction of the fifth

From the Department of Surgery, College of Medical Evangelists, Los Angeles Division.

1. Maumenee, A. E., and Kornblueth, W.: Symposium: Corneal Transplantation; Physiopathology, Tr. Am. Acad. Ophth. **52**:331-340, 1948.

2. Gross, R. E.; Bill, A. J., Jr., and Peirce, E. C., II: Methods of Preservation and Transplantation of Arterial Grafts: Observations on Arterial Grafts in Dogs; Report of Transplantation of Preserved Arterial Grafts in 9 Human Cases, Surg., Gynec. & Obst. **88**:689-701, 1949.

3. Kearns, J. E., Jr., and Reid, S. E.: Successful Homotransplantation of Skin from Parents to Son, Plast. & Reconstruct. Surg. **4**:502-507, 1949.

rib. During the entire operation each animal was given a slow intravenous infusion of 300 cc. of a 1% procaine hydrochloride solution. After exposure of the left lung, 1% procaine hydrochloride solution was injected into the pleura overlying the hilus and over the left vagus nerve just before it passes across the arch of the aorta. The left pulmonary artery was carefully dissected free from the overlying pleura. As long a segment of the artery as possible was isolated, but care was exercised not to penetrate the right pleural cavity. This accident if not recognized will cause the death of the animal. In our earlier experiments we resected the middle lobe because we believed it impossible to anastomose the small middle pulmonary vein. In later experiments the middle lobe was not resected but left in situ, and the branch of the pulmonary artery supplying it and the middle pulmonary vein were ligated in continuity. This left only three vessels to anastomose: the pulmonary artery, the inferior pulmonary vein, and the superior pulmonary vein. The first two vessels were generally large enough to be anastomosed satisfactorily to the recipient, but the superior pulmonary vein in the dog is usually small and therefore difficult to anastomose.

After clearing the pulmonary artery, the lung was turned over to expose its ventral aspect. In this way the superior pulmonary vein was exposed and isolated for as long a distance as possible. The inferior pulmonary vein was next exposed after the inferior pulmonary ligament was divided. The pleura covering the vein was divided, and the vein was dissected free. It was necessary to exercise great care, especially at this point, to avoid entering the opposite pleural cavity. The pleura on the ventral and dorsal aspects of the hilus was then incised in order to expose the bronchus. The adventitia between the bronchus and the pericardium was divided, and the main stem bronchus was cleared up to the region of the carina. The hilar structures were similarly treated and exposed in the second animal.

The decision as to which animal would be the donor and which the recipient depended upon a number of factors. The stronger-appearing animal and the one which seemed to have a better respiratory volume, rate, and rhythm was chosen as the recipient. The condition of the exposed lungs was also important. Trauma to the lungs was carefully avoided during dissection of the hilar structures. No clamps of any kind were placed on the lungs for traction. Other things being equal, the less traumatized lung was chosen for transplantation. The animal with the larger segments of hilar structures was preferred. The lungs of each animal were inflated every 20 minutes throughout the procedure to prevent atelectasis of the lung which was to be transplanted.

After the decision had been made regarding the donor and recipient animals, the lung was removed from the recipient animal. In so doing we endeavored to leave the longest possible lengths of blood vessels in the animals to make the anastomosis of the blood vessels easier. The bronchus was occluded with a noncrushing clamp. Bulldog arterial clamps shod with rubber were placed on the ends of the vessels in the recipient animal. Finally, the lung which was to be transplanted was removed from the donor animal. Care was taken to leave as long segments as possible of bronchus, artery, and veins attached to the lung to render less difficult the subsequent anastomoses. Bulldog clamps shod with rubber were placed on the vessels of the lung. The pulmonary artery was occluded first and divided, then the superior pulmonary vein, and finally the inferior pulmonary vein. The bronchus

was divided as close as possible to the carina. Heparin sodium (1,000 U. S. P. heparin units) was injected into the right ventricle of each animal a short time before the lungs were removed in order to prevent thrombosis within the pulmonary vessels at the sites of anastomoses.

The bronchus was anastomosed first, and interrupted mattress sutures of nylon thread were placed along the anterior and posterior walls. The lung was then inflated, and additional sutures were placed at points of leakage. These points of leakage could be detected by the sound of escaping air when the lung was inflated or by the appearance of small air bubbles along the suture line. The pulmonary artery, the superior pulmonary vein, and the inferior pulmonary vein were anastomosed in turn and in that order. The first row sutures posteriorly was of the continuous everting mattress type. Interrupted mattress sutures which everted

*Homologous Transplantation of the Lung: Results in Completed Transplants*

| Dog No. | Period of Survival After Transplantation | Changes in Transplanted Lung | | Cause of Death |
|---|---|---|---|---|
| | | Gross | Microscopic | |
| 137 | 20 min. | Atelectasis of entire lung | Atelectasis; no cellular reaction | Tension pneumothorax due to leakage from bronchial anastomosis |
| 150 | 18 hr. | Atelectasis; hemothorax | Early necrosis of alveolar septa and capillaries; no cellular reaction | Necrosis of transplant; thrombosis of superior pulmonary vein |
| 126 | 29 hr. | Atelectasis of upper lobe, edema of middle and lower lobes, hemothorax | Early necrosis of alveolar septa, alveolar edema, invasion by polymorphonuclear leukocytes | Hemorrhage from the inferior pulmonary vein |
| 135 | 80 hr. | Atelectasis of upper lobe, hemothorax | Early necrosis of alveolar septa and capillary walls; alveolar edema; invasion by lymphocytes and polymorphonuclear leucocytes | Hemorrhage due to heparin sodium overdosage |
| 164 | 8 days | Partially organized hemothorax with adhesions between transplant, parietal pleura, and pericardium | Pulmonary edema and invasion by polymorphonuclear leucocytes, many air-containing alveoli | Hemorrhage from leak at anastomotic site in the inferior pulmonary vein |

the intima were placed anteriorly. The suture material used was 00000 Deknatel. The superior pulmonary vein was the most difficult of the vessels to anastomose because of its small size. At the conclusion of the anastomosis, the clamps were removed from the superior pulmonary vein and from the inferior pulmonary vein. Finally the clamps were removed from the pulmonary artery. Additional sutures were placed at sites of leakage. The pleura was sutured over the line of anastomosis of the bronchus both anteriorly and posteriorly. The chest wall was closed in layers with a No. 50 cotton suture after the transplanted lung had been inflated and the chest aspirated. Postoperatively the animals were given 100,000 units of penicillin intramuscularly each day, 1,000 U. S. P. heparin units of heparin sodium twice daily for 3 days, and thereafter 1,000 units daily for 4 more days.

## RESULTS

The technic of homologous transplantation of an entire lung, which was finally developed and which is described here, enabled us to complete the operation in five animals (Table). Despite the complete severance of the nerve supply to the trans-

planted lung, the respiratory excursion was synchronous on the two sides, although it was relatively diminished on the side of the transplant. Certain peculiarities of respiration were observed. The animals exhibited paroxysms of dyspnea lasting one to two minutes. The respirations between these paroxysms, which occurred approximately once every 15 minutes, were deeper and more rapid than normal (30 per minute). From time to time the animal gave a deep cough suggesting the presence of bronchial irritation.

The results of homologous transplantation of the lung are shown in the Table. The appearance of foci of cellular infiltration in the transplants provides strong evidence that blood flow was reestablished through three of the five transplanted lungs. The deaths of the recipient animals were all due to technical errors committed during or after the operative procedures. These errors will be avoided as more experience with this operation is gained.

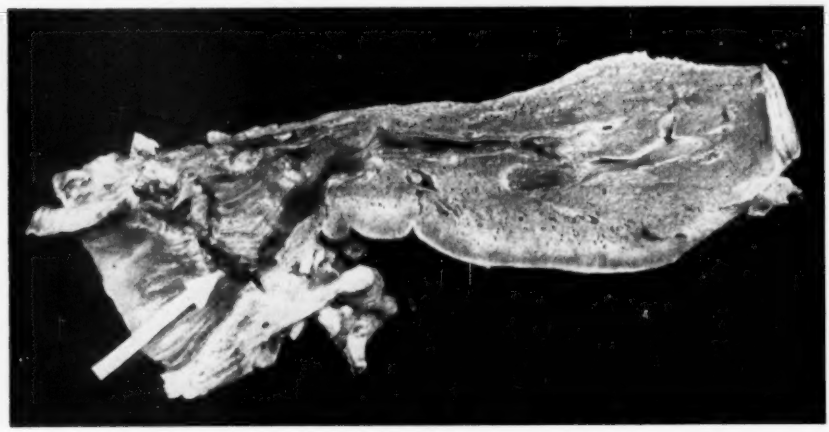

Fig 1.—Anastomosed bronchus; gross specimen removed eight days after homotransplantation. Firm union of subepithelial tissues of bronchus. Arrow points to demarcation line between epithelial lining of bronchus of recipient (left) and that of transplanted lung.

The bronchial anastomoses healed rapidly. In Dog No. 135, which survived for 80 hours (Table) after the transplantation, there was at the time of death an early proliferation of fibroblasts accompanied by numerous lymphocytes and polymorphonuclear leucocytes at the site of the bronchial anastomosis. The animal which survived for eight days (Dog 164) showed an advanced stage of healing of the bronchial anastomosis (Fig. 1). However, epithelial linings of the bronchi of the host and of the transplanted lung were still clearly demarcated. In this animal a partially organized hemothorax was present. Numerous adhesions had formed between the transplanted lung, the parietal pleura, and the pericardium (Fig. 2). The left pleural cavity contained a thick fibrinous cast. Many of the adhesions were fibrinous, but some consisted of well-vascularized fibrous tissue. While numerous alveoli were atelectatic or contained fluid, many were air-containing, particularly those in the lower lobe. Numerous polymorphonuclear leucocytes were

Fig. 2.—Gross specimen removed eight days after homotransplantation. Transplanted lung is to right. Note section removed from lower lobe of transplanted lung.

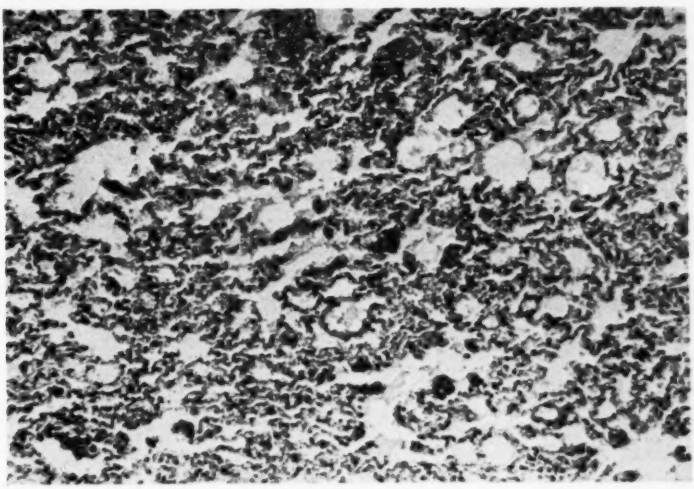

Fig. 3.—Homotransplanted lung; specimen removed eight days after homotransplantation. Edema fluid in some alveoli with lymphocytic and polymorphonuclear leucocytic infiltration. Many alveoli are air-containing. × 90.

present in the lumina of the blood vessels, in the bronchial lumina, and in the alveoli. The alveolar septa were well vascularized (Fig. 3).

Thrombosis of an anastomosed blood vessel, the superior pulmonary vein, occurred in only one animal. However, because of the small diameter of the vessels, the anastomosis not infrequently resulted in some narrowing of the lumen. This may have contributed to the lack of evidence of blood flow through the transplanted lung which was observed in one animal (Dog 150).

## COMMENT

The technical difficulties of homologous transplantation of the lung arose mainly in the earlier phases of this study, in which a total number of 34 dogs was used. However, once the technic was standardized, it was possible to complete the procedure five times out of the seven in which it was attempted. It will be noted, too, that there was a progressive lengthening of the survival time of these animals. These facts indicate that homotransplantation of one entire lung is from the viewpoint of surgical technic a perfectly feasible procedure. Thrombosis of the blood vessels at the sites of anastomosis did not present a problem, since it occurred in only 1 of the total of 15 vessels which were anastomosed.

The structural changes in the transplanted lungs must be discussed. In the animals with the shortest survival times, the chief changes were edema of the lungs with early necrosis of the alveolar septa. With longer survival (29 hours) of the host, cellular invasion of the transplant occurred. The cells were chiefly lymphocytes and polymorphonuclear leucocytes. If the animal survived long enough (8 days), evidences of vascularization of the lung appeared, with many of the alveoli showing the replacement of edema fluid with air.

What is the mechanism underlying these structural changes in the homotransplant? There are three possible causes: (1) ischemia of the lung between the time of its removal from the donor and its transplantation into the recipient; (2) inadequate blood flow through the lung after transplantation, and (3) the formation by the host of a specific antibody to the foreign tissue of the homotransplant. It has been demonstrated [4] that pulmonary tissue possesses considerable resistance to the ischemia resulting from occlusion of the pulmonary artery. In transplantation of the lung, however, the bronchial arteries as well as the pulmonary artery are occluded. The period of ischemia—that is, the period elapsing between removal of the lung from the donor and its transplantation into the recipient—varied in these experiments from one to two hours. Despite this, we suggest that while some of the structural changes may be attributed to ischemia during this time, they are not irreversible in character. This would be indicated by the fact that the changes appeared to decrease in severity with prolongation of the survival time. In addition, rapid healing of the bronchial anastomosis, as observed at the eighth day after operation, suggests that the early ischemia left no irreversible tissue damage. That blood flowed from the host into the blood vessels of the lung graft is shown by the appearance of cellular infiltration in the graft. It is difficult to state to what

4. Davis, H. A.; Gordon, W. B.; Hayes, E. W., Jr., and Wasley, M. T.: The Effects upon the Lung of Varying Periods of Temporary Occlusion of the Pulmonary Artery, A. M. A. Arch. Surg. **64**:464-474, 1952.

extent an antigen-antibody reaction [5] is responsible for the structural changes in the lung graft. The factors underlying the destruction of homologous transplants have recently been critically evaluated.[6]

We have already mentioned the remarkable rapidity with which the bronchial anastomosis healed (Fig. 1). It is probable that bronchial tissue is more resistant to ischemia than is pulmonary tissue. This would explain the healing of the bronchial anastomosis in spite of the period of ischemia which unavoidably occurred during the procedure of transplantation.

SUMMARY

Homologous transplantation of the lung has been performed in dogs. A procedure has been developed and described which is feasible from the viewpoint of surgical technic. The functional behavior of, and the structural changes in, the homotransplanted lungs are described.

5. Medawar, P. B.: Immunity to Homologous Grafted Skin: III. The Fate of Skin Homografts Transplanted to the Brain, to Subcutaneous Tissue and to the Anterior Chamber of the Eye, Brit. J. Exper. Path. **29**:58-69, 1948.

6. Longmire, W. P., Jr., and Smith, S. W.: Homologous Transplantation of Tissues: A Review of the Literature, A. M. A. Arch. Surg. **62**:443-454, 1951.

# POSTERIOR TRIANGLE OPERATIONS AND TRAPEZIUS PARALYSIS

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IN THE past 12 months I examined six patients who had injuries to the accessory nerve secondary to minor surgical procedures carried out in the posterior cervical triangle. In only two of the six patients did the referring physician recognize the existing trapezius paralysis or appreciate how disabling this paralysis may be. As pointed out by Norden,[1] Wulff,[2] and Hanford,[3] the accessory nerve is extremely vulnerable to injury, since it traverses the posterior cervical triangle from the posterior edge of the sternomastoid muscle to its entrance into the superior edge of the trapezius. The nerve trunk is small and lies rather superficially beneath the skin. The operator rarely recognizes that it has been injured in the course of minor surgical procedures.

It is probable that this complication occurs much more frequently than seems apparent by perusal of the surgical literature. Norden reported 16 cases in which paresis occurred in six patients at the time of operation for tuberculous lymphadenitis, in four at operation for undefined lymphomas, in another four at biopsy, in one during section of the scalenus muscle, and in one with blunt injury over the course of the accessory nerve. Wulff [4] reported a 3% incidence of accessory nerve paralysis (230 neck dissections) and Hanford [5] a 6% incidence in the course of operation for tuberculous lymphadenitis.

The clinical picture of trapezius palsy secondary to accessory nerve injury is illustrated in the six patients under discussion. Of these one had a small sebaceous cyst, one had a normal lymph node, one had a pathological diagnosis of fibrosis of a lymph node and one showed normal skin at the time of pathological study, and two showed evidence of tuberculous lymphadenitis. All patients complained of a dull aching pain and a sensation of soreness or stiffness in the shoulder on the side of the operative procedure. The pain may come on immediately after operation or develop when the patient resumes his usual activities. Pain was always increased by exertion. Patients also complained of inability to elevate the shoulder fully and to abduct the arm from the side above the horizontal position. The neurological picture is clearly defined. The affected shoulder is lower than the opposite shoulder and appears notched by loss of the superior muscle fibers (Fig. 1). The scapular

From the Division of Physical Medicine, Washington University School of Medicine.

1. Norden, A.: Peripheral Injuries to the Spinal Accessory Nerve, Acta chir. scandinav. **94**:515-532, 1946.

2. Wulff, H. B.: The Treatment of Tuberculous Cervical Lymphoma: Late Results in 230 Cases Treated Partly Surgically, Partly Radiologically, Acta chir. scandinav. **84**:343-366, 1940.

3. Hanford, J. M.: Surgical Excision of Tuberculous Lymph Nodes of the Neck, S. Clin. North America **13**:301-310, 1933.

4. Wulff.[2]

5. Hanford.[3]

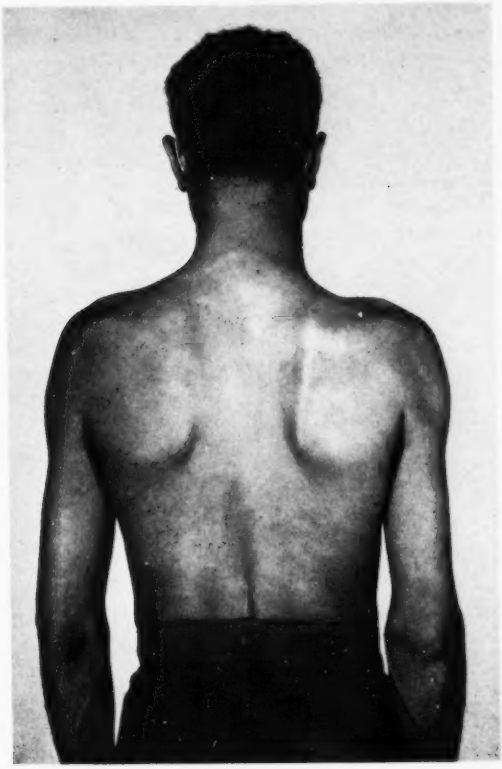

Fig. 1 (Case 5).—Note notching of upper right shoulder profile and sharpness of scapula.

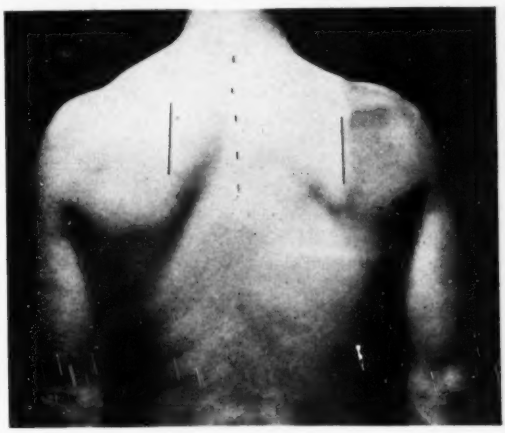

Fig. 2 (Case 3).—Trapezius winging. Scapula is displaced laterally but not significantly lowered. This contrasts sharply with serratus and rhomboid winging.

outlines stand out clearly, and the scapula is displaced laterally when compared with the normal side (Fig. 2). The levator scapulae and the rhomboids stand out clearly. The patient is unable to abduct the shoulder above 90 degrees because of poor scapular fixation, and the humerus goes into internal rotation as this maneuver is attempted (Fig. 3). Periarthritis of the shoulder joint often follows and may confuse the examiner. Electrical diagnostic testing is a valuable confirmatory procedure.

In terms of therapy, obviously, the best measure is prevention of this disabling accident. The posterior cervical triangle should never be the site of an elective operative procedure if any reasonable alternative exists. If procedures must be carried out at this site, electrical stimulation should be used to isolate and identify the nerve, as described and advocated by Lahey.[6] In 4 of the 14 cases reported by

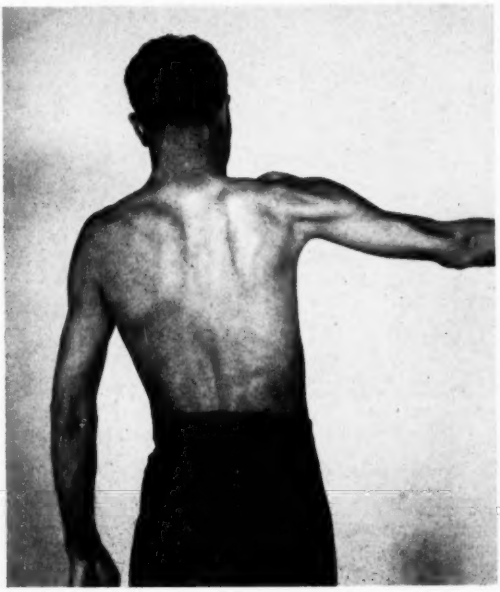

Fig. 3 (Case 5).—Patient is vainly attempting to elevate extremity (180 degree abduction). Humerus is internally rotated and scapula poorly fixed. Shoulder abductors are entirely normal.

Norden,[1] nerve suture was attempted. In two of these cases restoration of function was complete. Early suture after recognition of this disability, as recommended by Holmes and Young,[7] seems to be the procedure of choice. No adequate fascial suspension or muscle substitution procedure has been reported.

## REPORT OF CASES

CASE 1.—L. C., a 49-year-old salesman, was operated on on Feb. 20, 1950, for removal of a sebaceous cyst in the lower posterior triangle of the right side of the neck. The patient suffered

6. Lahey, F. H.: Radical Dissection of the Neck, S. Clin. North America **29**:631-640, 1949.

7. Holmes, W., and Young, J. Z.: Nerve Regeneration After Immediate and Delayed Suture, J. Anat. **77**:63-96, 1942-43.

severe pain for three weeks after operation and had difficulty in moving his shoulder. Physical examination on May 2 showed severe atrophy of the right trapezius muscle. There were some persisting fibers of innervated muscle in the trapezius, but elevation was largely carried out by the musculus levator anguli and the musculus scapulae. Electrical excitability tests showed a reaction of degeneration in the trapezius. No follow-up information was available.

CASE 2.—V. A., a 40-year-old housewife, had biopsy of the left cervical lymph node performed on June 6, 1950. The condition was diagnosed as a possible reticulum cell sarcoma, and another biopsy was suggested. A diagnosis of trapezius paralysis was made six weeks postoperatively. Physical examination on July 26 revealed the typical findings of trapezius paralysis. Electrical excitability tests showed a reaction of degeneration in the trapezius. In addition, some periarthritis, manifested by marked limitation of motion, pain, and tenderness, was present. A subsequent examination, on Jan. 17, 1951, showed definite sagging of the left shoulder girdle, atrophy of the left trapezius muscle and muscles of the left shoulder girdle, some pain, and inability to raise the arm above the horizontal position. There was, however, definite improvement from the patient's original condition.

CASE 3.—A. S., a 31-year-old man employed as a machinist, showed the first evidence of reactivation of Hodgkin's disease in the past seven years on examination in September, 1950. On Sept. 19, a biopsy of the right cervical lymph node was performed, and on Sept. 30, the pathological diagnosis was fibrosis. On Dec. 5, a physical examination was made, with a diagnosis of trapezius paralysis secondary to biopsy of the cervical lymph node. Reaction of degeneration was present in the right trapezius. The patient had a dull aching pain that was occasionally bothersome Neurological examination on Dec. 16 revealed atrophy of the right trapezius. A subsequent neurological examination, on Jan. 22, 1951, showed that the right trapezius was entirely functionless, with complete atrophy. The patient refused surgical anastomosis.

CASE 4.—L. V. R., a 27-year-old man employed as a drapery cutter, had a basic diagnosis of psychoneurosis. A presumed cyst in the left posterior cervical triangle was removed, with resulting trapezius paralysis. There was a "fair" return of function in a few days. On pathological examination the so-called cyst proved to be normal skin. The patient showed a complete reaction of degeneration on tests for excitability.

CASE 5.—C. G., a 46-year-old man employed as a laborer, on March 1, 1950, underwent surgery for the removal of a lymph node in the right posterior cervical triangle. Physical examination on May 7, revealed atrophy and loss of trapezius function in the right shoulder girdle and preservation of other functions. The patient's inability to abduct and elevate the shoulder resulted from poor scapular fixation. There was a complete reaction of degeneration.

CASE 6.—M. M., a 39-year-old woman employed as a clerk, underwent an otolaryngologic examination on Feb. 13, 1951, which showed an enlarged and palpable lymph node in the posterior triangle. Biopsy of the lymph node was performed on Feb. 28, and the pathological report was tuberculous lymphadenitis. On March 13, physical examination revealed partial paralysis of the right trapezius, with the upper division affected more than the middle and lower divisions. Electrical tests showed a reaction of degeneration in the upper division of the trapezius and a mixed reaction in the two lower divisions. The patient was unable to fix the scapula properly in order to carry out complete abduction and elevation; however, she did not have scapular winging. A subsequent physical examination, on Aug. 3, 1951, showed that the patient had a recurrence of pain but was able to work. She had a little hollowing of the trapezius edge and a peculiar abduction pattern with an inability to fixate the scapula. Complete elevation and forward flexion were somewhat restricted.

## SUMMARY

Six cases of inadvertent accessory nerve injury from minor procedures in the posterior triangle are presented.

Literature, incidence, clinical findings, prevention, and treatment are discussed.

This disabling accident is so common that elective operative procedures in the posterior triangle should never be carried out if there is a reasonable alternative.

# PARTIAL GASTRECTOMY WITH AND WITHOUT VAGUS RESECTION IN TREATMENT OF DUODENAL ULCER

## Comparative Analysis of Results of Gastrectomy Alone and Combined with Infradiaphragmatic Vagus Resection

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R. E. PAUL, M.D.
AND
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DES MOINES, IOWA

THERE has existed for many years a difference in opinion as to the type of surgical procedure which would be most efficacious in those cases of duodenal ulcer in which surgical treatment is required. Until the reports of Dragstedt in 1943 concerning the value and indications for vagotomy in the treatment of duodenal ulcer, the majority of surgeons in this country were performing a partial gastrectomy as the procedure of choice, with a high percentage of favorable results. The reintroduction of this operation of dividing or resecting a portion of the vagus nerves resulted in many surgeons and surgical groups adopting this form of surgical therapy in a large number of their cases.

During a period of about seven years, at least 4,000 vagotomies, or vagus resections, were performed in this country. The preliminary reports from various areas were favorable; however, many of these surgeons have now returned to their previous operation, partial gastrectomy, in preference to a vagus neurectomy.

Prior to 1947 and since 1949, we have performed a partial gastrectomy which removed approximately 75% of the stomach, including the pyloric antrum and that portion of the duodenum containing the ulcer and associated fibrosis. The anastomosis has been of the antecolic type, with a short afferent loop to the lesser curvature side of the stomach. This group represents over 100 cases.

In 1947 we combined our routine type of partial gastrectomy with a bilateral infradiaphragmatic vagus resection in 30 cases. During this time, a careful and frequent inpatient follow-up study was carried out in both groups. This report includes a comparative analysis of the results of 99 cases of partial gastrectomy with the results of 30 cases of partial gastrectomy combined with a bilateral infradiaphragmatic vagus resection. In the former group, the follow-up studies were conducted for a period from 6 to 54 months, whereas in the latter group the follow-up was from 6 to 48 months.

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

It is intended that this presentation be considered a preliminary report, since it is our opinion that the results of treatment of peptic ulcer must be based on an adequate and extended follow-up covering many years.

The average age of the patients was 45.5 years in the partial gastrectomy group and 47.3 years in the other group (Table 1). All the patients were men, from 21 to 72 years of age. The greatest number, representing 61 (61.6%) in the partial gastrectomy series as compared with 20 (66.6%) in the combined gastrectomy-vagectomy series, were in the 40 to 59 age group.

The average duration of symptoms prior to definitive surgery was 8.6 years in the partial gastrectomy series and 11.8 years in the vagectomy series.

TABLE 1.—*Incidence According to Age*

| | Partial Gastrectomy | | Partial Gastrectomy and Vagectomy | |
|---|---|---|---|---|
| Age | No. | % | No. | % |
| 20-29 | 11 | 11.2 | 3 | 10 |
| 30-39 | 17 | 17.2 | 7 | 23.35 |
| 40-49 | 24 | 24.2 | 5 | 16.65 |
| 50-59 | 37 | 37.2 | 15 | 50 |
| 60 and over | 10 | 10.2 | 0 | 0 |
| Totals | 99 | 100 | 30 | 100 |

TABLE 2.—*Complications of Ulcer and/or Surgical Procedures Prior to This Study*

| | Partial Gastrectomy Group * | | Partial Gastrectomy and Vagectomy Group | |
|---|---|---|---|---|
| | 99 Cases | | 30 Cases | |
| Type | No. | % | No. | % |
| Gastroenterostomy | 6 | 6.06 | 3 | 10 |
| Hemorrhage, massive | 40 | 40.4 | 13 | 43.4 |
| Perforation of ulcer | 20 | 20.7 | 8 | 26.6 |
| Vagotomy | 1 | 1 | 0 | .. |
| Totals | 67 | 68.1 | 24 | 80 |

* One patient in this group had a combination of these complications.

Of the patients in the group upon whom a partial gastrectomy was performed, 67 (66.5%) had previous surgery or complications as a result of their ulcer, as compared with 24 (80%) in the other group (Table 2.).

## RESULTS

The follow-up was obtained for 72 (72.7%) of the patients in the partial gastrectomy group and for 26 (89.6%) in the partial gastrectomy and vagectomy group. These patients were admitted to the hospital for complete and comprehensive follow-up studies at intervals of six months for the first two examinations and yearly thereafter. The average follow-up period was 28.2 months for the partial gastrectomy cases and 32.6 months for the other group.

There were three (3.1%) postoperative deaths in the partial gastrectomy series and one (3.3%) in the gastrectomy-vagectomy group. Of the three deaths in the former group, one occurred on the 6th day and was due to pulmonary thrombosis;

one was the result of gastric hemorrhage on the 2d postoperative day, and one occurred on the 26th day as a result of pulmonary embolism. The only death in the latter group occurred on the 9th day and was due to duodenal perforation and generalized peritonitis.

TABLE 3.—*Associated Surgical Procedures*

| Operations | Partial Gastrectomy Group | | Gastrectomy-Vagectomy Group | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Appendectomy | 2 | 2.02 | .. | ... |
| Cholecystectomy | 1 | 1 | .. | ... |
| Cholecystojejunostomy | 1 | 1 | 1 | 3.3 |
| Cholecystotomy with removal of calculi | 1 | 1 | 1 | 3.3 |
| Diverticulum, duodenal, traction, resection of | 4 | 4.04 | 2 | 6.6 |
| Excision of marginal ulcer and resection of gastroenterostomy | 3 | 3.03 | 2 | 6.6 |
| Meckel's diverticulectomy | 1 | 1 | .. | ... |
| Resection of gastroenterostomy | 2 | 2.02 | 1 | 3.3 |
| Ventral herniaplasty | 2 | 2.02 | .. | ... |
| Totals | 17 | 17.1 | 7 | 23.3 |

TABLE 4.—*Postoperative Complications*

| Type of Complication | Partial Gastrectomy (99 Cases) No. | Gastrectomy-Vagectomy (30 Cases) No. |
|---|---|---|
| Abscess, intraperitoneal | 2 | .. |
| Atelectasis | 8 | 1 |
| Bleeding, gastric | 2 | 2 |
| Cardiac decompensation | 1 | .. |
| Cerebral hemorrhage | 1 | .. |
| Hematoma, wound | 1 | .. |
| Hemorrhagic pericarditis, traumatic | .. | 1 |
| Homologous serum jaundice | 1 | 1 |
| Jaundice, transient | 2 | .. |
| Jejunal (stomal) ulcer | 1 | .. |
| Obstruction, efferent loop, jejunum | 2 | 1 |
| Perforated duodenal stump | 2 | 3 |
| Peritonitis, acute | 1 | 3 |
| Pneumonia | 2 | .. |
| Pulmonary embolism or thrombosis | 2 | .. |
| Shock, secondary to gastric hemorrhage | 1 | .. |
| Thrombophlebitis, acute, leg and foot | 2 | .. |
| Urinary retention and cystitis | 1 | .. |
| Totals | 32 | 12 |

In 17 (17.1%) of the patients in the partial gastrectomy series, additional surgical procedures were performed to remove associated pathology, whereas in the gastrectomy-vagectomy series 7 (23.3%) patients required other surgical procedures (Table 3).

Thirty-two postoperative complications developed in 28 (28.2%) patients of the partial gastrectomy group and 12 complications in 9 (30%) patients in the group who had the combined procedure (Table 4). Of the total number of complications of both series, seven resulted in the deaths of four patients. Pulmonary complications were the most frequent in the former group, whereas duodenal leakage and associated peritonitis occurred more frequently in the latter group.

Postoperative gastric analysis studies in 56 (77.7%) patients in the partial gastrectomy group revealed no free acid in the fasting specimen in 51 (91%) and none after the administration of histamine in 35. In five cases, the fasting gastric specimen revealed 1 to 40 units of free acid. In 21 patients there was an increase of free acid from 1 to 40 units after injection of histamine. Of the 19 (65.5%) patients who had complete postoperative gastric analysis studies in the gastrectomy-vagectomy group, 19 (100%) had a complete and persistent absence of free hydrochloric acid in the fasting specimen, after Hollander's insulin test and after injection

TABLE 5.—*Results of Follow-up Study*

| | Partial Gastrectomy (72 Cases) No. | Gastrectomy-Vagectomy (29 Cases) No. |
|---|---|---|
| **Weight Gain** | | |
| Yes | 48 | 12 |
| No | 23 | 9 |
| Loss | 0 | 7 |
| **Abdominal Pain as Before Surgery** | | |
| Yes | 2 | 2 |
| No | 70 | 16 |
| Slight | 0 | 5 |
| **Appetite** | | |
| Excellent to good | 63 | 23 |
| Fair | 7 | 6 |
| **Nausea and/or Vomiting** | | |
| None | 63 | 20 |
| Occasionally | 7 | 6 |
| **Diet** | | |
| Ulcer or modified diet | 14 | 8 |
| Nonrestricted diet | 55 | 21 |
| **Bowel Habits** | | |
| Normal | 59 | 18 |
| Constipated | 7 | 0 |
| Diarrhea | 5 | 1 |
| Changing habits (diarrhea-constipation) | 1 | 7 |
| **Dumping Syndrome** | | |
| Severe | 1 | 1 |
| Moderate | 5 | 2 |
| Mild | 7 | 3 |

of histamine. In only one patient of this group was there an increase of free acid from 0 to 6 degrees after administration of histamine. The 12-hour fasting gastric secretion volume studies performed in the last follow-up of ten patients in this group showed an average of 367 cc. with an absence of free hydrochloric acid.

Of the followed patients, 68% gained weight and 32% showed no gain following partial gastrectomy. In the patients who had the combined operative procedure, 43% gained weight, 25% lost weight, and 32% remained the same. Of the former group 97% were relieved of their ulcer pain, and in the latter group 70% were relieved of their ulcer pain, 22% complained of slight pain, and 8% stated the pain was the same as it was preoperatively (Table 5).

In the partial gastrectomy group 80% of the patients were free from dietary restrictions, and 20% followed a modified diet. In the other group, 72% were

able to follow an unrestricted diet, and 28% were on a modified diet. In 88% of the partial gastrectomy group, the patients experienced a good appetite, as compared with 80% in the combined group.

Ninety per cent were free from nausea and vomiting, whereas the remainder complained of occasional gastric upset, particularly after overeating. In the other group, 77% did not complain of nausea or vomiting; however, 23% were distressed after overeating or partaking of food high in carbohydrates (Table 5).

The dumping syndrome was severe in one patient, moderate in five, and mild but controllable in seven in the partial gastrectomy group, an incidence of 18%. In the gastrectomy-vagectomy series, the dumping syndrome was severe in one patient, moderate in two, and mild in three, representing an incidence of 20.6%. Of the patients in the former group, 65% did not require frequent feedings, whereas 31% required more than three meals a day to maintain or gain weight. In the

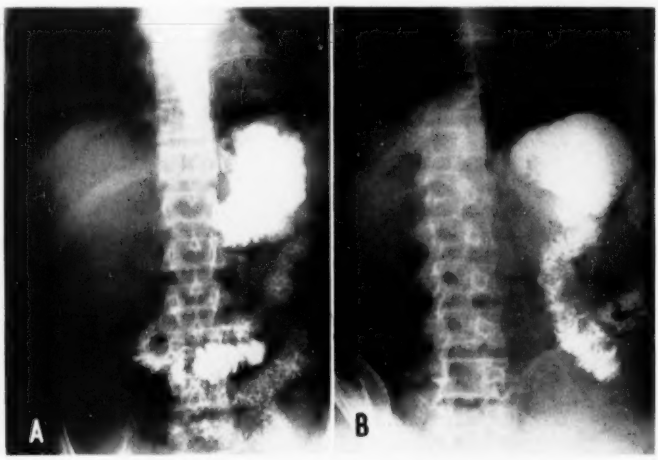


Fig. 1.—Postoperative barium studies of stomach and small bowel after combined procedure (*A*) and after partial gastrectomy (*B*). Roentgenograms were taken shortly after filling of stomach remnant with barium.

latter group, 48% did not require more than three meals a day, 48% required four to six meals per day, and 4% were partaking of more than 6 meals each day.

Postoperative follow-up gastrointestinal roentgenographic examinations revealed a satisfactory functioning stoma with no evidence of obstruction in both group studies. The average emptying time of the gastric remnant in the partial gastrectomy series in 61 patients studied was 45 to 90 minutes. In the series of patients upon whom a partial gastrectomy and vagectomy were performed, in every instance the remaining portion of the stomach revealed dilatation and atonicity shortly after surgery. These changes became less apparent upon subsequent follow-up studies, although in the late follow-up studies a delayed emptying of the gastric remnant occurred in 62.4% of these patients. In 37.5% there was a gastric residue after six hours, 4.1% showed retention at four hours, and 20.8% revealed barium in their stomachs at three hours. The average emptying time of the gastric remnant in this group was four hours (Figs. 1, 2, 3, and 4).

The motor barium intestinal roentgenographic studies of the patients in the gastrectomy-vagectomy series revealed the barium column in the cecum or ascending colon in five hours in 33.3% of the patients studied and in less than four hours in

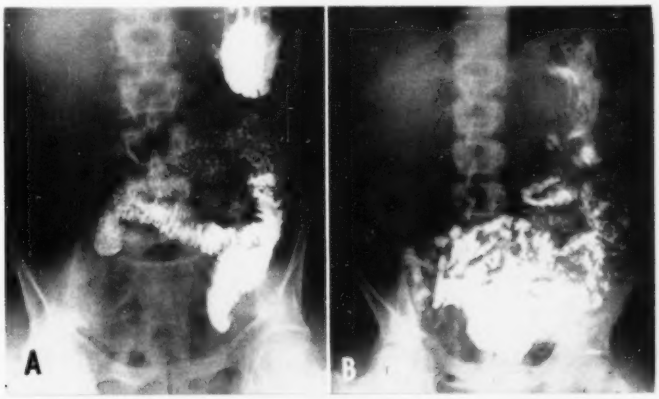


Fig. 2.—Roentgenograms made one hour after a barium sulfate meal in a case in which a combined procedure was carried out (*A*) and one in which partial gastrectomy was performed (*B*). Delayed emptying of barium from gastric remnant and associated gastroplegia are revealed in *A* as compared with *B*, in which a more rapid emptying has occurred and gastroplegia is absent.

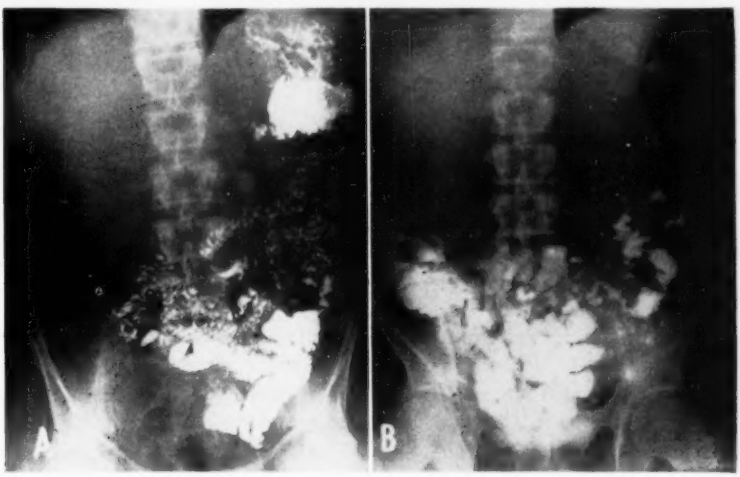


Fig. 3.—Roentgenograms made two hours after a barium sulfate meal in a case in which a combined procedure was carried out (*A*) and one in which partial gastrectomy was performed (*B*). Note the amount of barium in the small bowel and the stomach in *A*. In *B* the stomach is completely empty and there is evidence of barium in the ascending colon.

37.5% of the cases (Figs. 1, 2, 3, and 4). In 8 (33.3%) of these patients there was segmentation, clumping, and abnormalities of the small bowel pattern, particularly in the lower jejunum and upper ileum. These changes have persisted over a

periodic x-ray survey. The remainder of the series had a normal motor meal pattern and normal transit time.

A marginal, or stomal, ulcer developed in two patients, an incidence of 2.7% in the partial gastrectomy group. In the other group a stomal, or marginal, ulcer did not occur.

Gastroscopy was performed in 15 of the patients of the gastrectomy-vagectomy group during the follow-up studies. Of this number 14 revealed gastritis, and in 1 patient the gastric mucosa appeared normal. Five (37.5%) of this group had a severe gastritis. However, the majority of these patients apparently had no complaints as a result of the gastritis. Three of the patients who had severe gastritis also had gastrointestinal complaints and experienced the dumping syndrome.

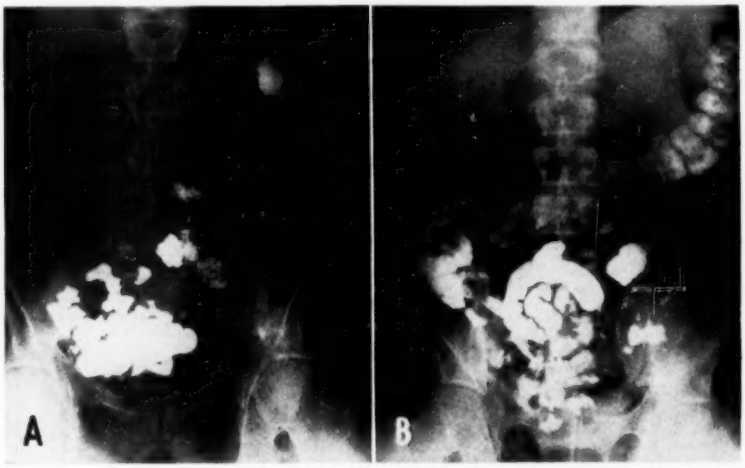


Fig. 4.—*A*, roentgenogram made six hours after a barium sulfate meal in a case in which a combined procedure was carried out. Note small amount of barium in the stomach and the remainder in the terminal loops of small bowel. *B*, roentgenogram made three hours after a barium meal in a case in which partial gastrectomy was performed. Complete emptying of the stomach is seen, with barium in the colon and small bowel.

## COMMENT

In review of the findings and complaints noted in the results of both groups of patients, general improvement of the patient with relief of the symptom complex of the peptic ulcer syndrome occurred in 87% of the patients followed in the partial gastrectomy series and in 78% of those in the partial gastrectomy-vagectomy series.

The remaining number in both groups had a variety of complaints, such as nausea and vomiting, failure to gain weight, dietary restrictions, mild epigastric pains, and dumping syndrome. In the partial gastrectomy-vagectomy series the number of patients having complaints was larger in each category and their distress probably was greater. This was particularly true in disturbance of bowel habits. There were a greater number who had diarrhea which was frequent enough to cause physiological disturbances and loss of weight. The diarrhea in this group was persistent in that it was unchanged over a period of years.

It is interesting to note that there was a complete and persistent absence of free hydrochloric acid, even after the administration of histamine and Hollander's insulin tests, in all patients in the partial gastrectomy-vagectomy group. This finding was not present in all patients of the partial gastrectomy series. In many patients the follow-up in the vagectomy series was for two to four years. It is assumed from these findings and studies that the vagectomy in this series of cases was complete. There is no evidence of regeneration at this time.

Combining a bilateral vagectomy with the same type of partial gastrectomy has resulted in a delay in the average emptying time of the gastric remnant from about one hour to four hours. The motor meal transit time was disturbed because of hypomotility in one-third of the patients studied. In addition, the small bowel pattern was abnormal because of segmentation and clumping of the barium in the lower jejunum and upper ileum.

The mortality was not increased by the addition of vagectomy to partial gastrectomy. The complication rates were almost equal in the two series. However, there were two complications which were directly a result of the vagectomy procedure: dysphagia due to injury to the muscular layers of the lower esophagus, and hemorrhagic pericarditis, probably traumatic, from mobilization of the vagus nerves.

In both series a short antecolic afferent loop, measuring about 4 in. (10 cm.) in length, has not resulted in any obstruction to the transverse colon and has not interfered with a normal functioning stoma. This antecolic anastomosis is simpler to perform and less hazardous, and, if further surgery is required, this type can be taken down more readily than a retrocolic anastomosis.

## SUMMARY AND CONCLUSIONS

A comparative study of the results of partial gastrectomy in 99 patients and the results in partial gastrectomy with bilateral infradiaphragmatic vagus resection in 30 patients treated for duodenal ulcer is presented. In both groups the duodenal ulcer was removed, and the type and amount of gastric resection were identical in the two. An antecolic gastrojejunal anastomosis was performed, with use of a short afferent jejunal loop.

The postoperative mortality (3%) was the same in the two series. The complication rate was likewise about equal (30%).

The postoperative gastric analysis studies revealed absence of free hydrochloric acid in the fasting specimens in 91% of the partial gastrectomy group and in 100% in the gastrectomy-vagectomy group. After injection of histamine, the gastrectomy group showed 1 to 40 units of free hydrochloric acid in 37% of the patients. In the gastrectomy-vagectomy group, after administration of histamine and Hollander's insulin tests, there was a complete absence of free hydrochloric acid.

The emptying time of the gastric remnant in the partial gastrectomy series averaged one hour, and in the other group the average time was four hours. In 33.3% of the patients studied in the gastrectomy-vagectomy group, the motor meal studies revealed hypomotility of the small bowel with puddling, clumping, and segmentation of barium in the lower jejunum and upper ileum.

Two cases (2.7%) of marginal ulcer developed in the partial gastrectomy group and none in the other group.

The over-all results were considered excellent to good in 87% of the partial gastrectomy group and in 78% in the gastrectomy-vagectomy group. The dumping syndrome occurred equally often (20%) in the two series. The most troublesome complaint and complication was diarrhea (30%) in the gastrectomy-vagectomy series.

The end-results of this antecolic anastomosis are comparable to those reported in a series in which a retrocolic anastomosis was performed.

Dr. Paul Trier, Department of Radiology, cooperated in obtaining and interpreting the follow-up radiologic studies on these patients.

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# SIMPLE ONE-STAGE METHOD OF HEPATECTOMY IN THE DOG

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THE METHOD to be described in this paper is an extension of that of Markowitz, Yater, and Burrows.[1] The introduction of silicone by our colleague, Jacques, and the availability at surgical supply houses of blood vessel suture ready for use, together with considerable experience over the past two decades, has prompted us to publish this method in its present form.

The operation of hepatectomy in the dog is a difficult technical procedure. When badly done the operation results in hemorrhage and shock; any studies made have to be considered in the light of these complicating factors. When done well hepatectomy results in a preparation that is seemingly normal for at least 12 hours; the duration of survival and the postoperative behavior following this time depend upon such uncontrollable circumstances as prothrombin, bleeding, and the general viability of the animal that has been selected essentially at random. Although the liver is said to have 500 known functions (Bollman [2]), many of these functions have been deduced from studies on liver slices, from the effects of disease in the human being, and from ingenious ratiocination. Before any function of the liver can be definitely established, it would seem essential to study the matter in question on the surviving organism after hepatectomy. It is one of the glories of the Mayo Foundation that a member of its laboratories first worked out a dependable procedure for removing the liver in such a manner that the resulting dog seemed normal for many hours before it died.

Over a period of time we have required a supply of liverless dogs prepared under conditions which preclude the use of animals prepared according to Dr. Mann's three-stage method. Moreover, when an investigator is concerned with a problem that should be solved in an academic year, the use of the Mayo Foundation method is impracticable. For reasons of expense also, we submit this method of hepatectomy which, while it involves a compromise everywhere, results in preparations that seem normal for many hours after removal of the liver. The method is

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1. Markowitz, J.; Yater, W. M., and Burrows, W. H.: J. Lab. & Clin. Med. **18**:1271, 1933.

2. Bollman, J. L.: Personal communication to the authors.

based upon two previously published technics for hepatectomy: (1) the technic of doing an Eck fistula,[3] as done at the Mayo Foundation, and (2) the method of Firor and Stinson,[4] who used a Y-shaped pyrex® glass cannula introduced into the portal vein and vena cava below and above the liver, respectively. Firor and Stinson made the odd observation that blood flowing through a pyrex® tube does not clot. Strange as it may seem, this fact is true. If this Y-shaped glass cannula is made of soft glass, the animals die on the operating table because of thrombosis in the tubing. The chief disadvantage of their procedure is that, while surgically practicable, it results in a preparation that has suffered all the elements of shock, owing to complete obstruction of the portal vein and inferior vena cava for at least 10 and possibly 15 minutes. Such a preparation may recover smartly after the cannulation, so that one may study the physiology of hepatic insufficiency. However, the animals do not live long and in the case of young subjects do not recover from the obstruction properly.

The introduction of the use of silicone by our colleague, Jacques, has rendered less unphysiological the principles underlying our method of hepatectomy. It is possible to introduce a siliconed pyrex® glass cannula into the inferior vena cava in such a manner as to reconstitute it so that the liver may be removed without obstructing the circulation from the posterior half of the body for more than two minutes. The rapid performance of an Eck fistula below this cannula makes it possible to dispose of the portal circulation without obstruction at any time. With these two ideas in mind, it is possible to perform at one sitting a complete hepatectomy in animals, with a minimum of physiological disturbance. In general, such animals resemble in their postoperative behavior those described by F. C. Mann and his school,[5] with the exception that hypoglycemia sets in earlier in our preparations. This difference is probably due to the fact that Dr. Mann's animal lives for some months during which it has an Eck fistula. Eck fistula animals have a higher glycogen content in the muscles, which possibly may result in a delayed fall in blood sugar after hepatectomy. When the liver is removed by the one-stage method, the blood sugar falls to a convulsive level in two to three hours.

The essential gadget used in the operation of hepatectomy in the dog is a siliconed pyrex® glass cannula about the size of a rather large cigarette, with a beveled end. A piece of thread is tied at the unbeveled end (Figs. 1, 2, 3, 4, 5, and 6). The hepatorenal ligament is cut, and the cannula is introduced into the inferior vena cava after a temoporary obstructive ligature of this vein is tied above the adrenal gland. The total obstruction should not last more than two minutes and often has lasted only 60 seconds. When the siliconed cannula has thus been introduced and tied in position by two previously placed ligatures about the inferior vena cava, the obstructive ligature is sectioned. An Eck fistula is rapidly performed below, as described elsewhere.[6] Prior to the beginning of the Eck fistula, two stout ligatures made of fishing-reel cable are placed around the structures in the lesser omentum but left untied. When the Eck fistula has been completed, these ligatures are tied. A Carmalt clamp

3. Fishback, F. C.: Ann. Surg. **86**:436, 1927.

4. Firor, W. M., and Stinson, E., Jr.: Bull. Johns Hopkins Hosp. **44**:138, 1929.

5. Mann, F. C.: Am. J. M. Sc. **161**:37, 1921.

6. Markowitz, J.; Lotto, W.; Archibald, J., and Downie, H. G.: To be published.

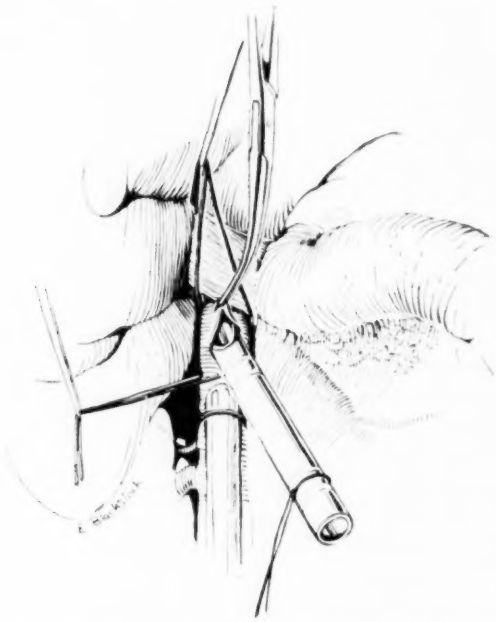

Fig. 1.—Introduction into inferior vena cava of siliconed pyrex® cannula with beveled end (hepatorenal ligament has been cut). Thumb should occlude opening to minimize air embolism and should be pushed well into vena cava. Traction on thread causes bottom end to engage against occluding ligature, which has been previously tied over a rod to facilitate its rapid section as soon as threads have been tied above and below nick in vena cava.

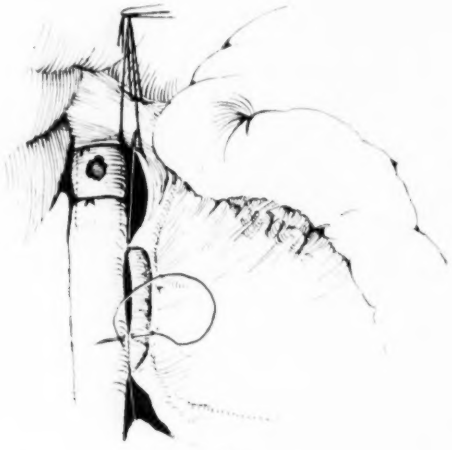

Fig. 2.—Two loose ligatures are placed about gastrohepatic omentum. After presenting part of fascia is freed, portal vein is aligned to vena cava by two stay sutures. Posterior suture is laid with the bottom needle.

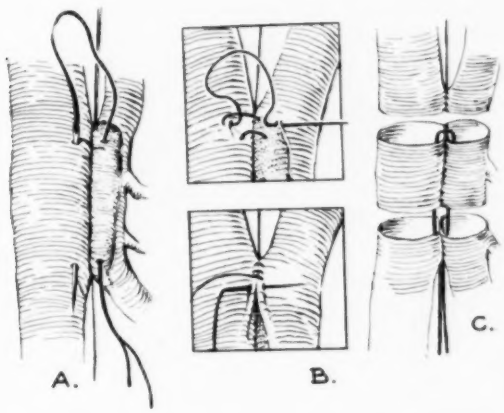


Fig. 3.—*A*, cutting thread is introduced as shown. *B*, upper, the cutting thread is buried by an anterior suture line, the first bite of which is a generous stitch into inferior vena cava; lower, this continues around entrance and exit of cutting thread at the bottom of fistula. *C*, principle of action of cutting thread is shown. When this is seesawed out, there will be no bleeding if suturing has been snug about entrance and exit.

Fig. 4.—Ligatures around gastrohepatic omentum are securely tied beyond last venous branch. Structures are cut distal to ties. Carmalt clamp being placed on hepatic side to prevent reflux bleeding.

Fig. 5.—Left coronary ligament has been divided almost to vena cava. Bleeding point on diaphragm has been picked up; it should be tied or electrocoagulated. Similarly right and median coronary ligaments are severed.

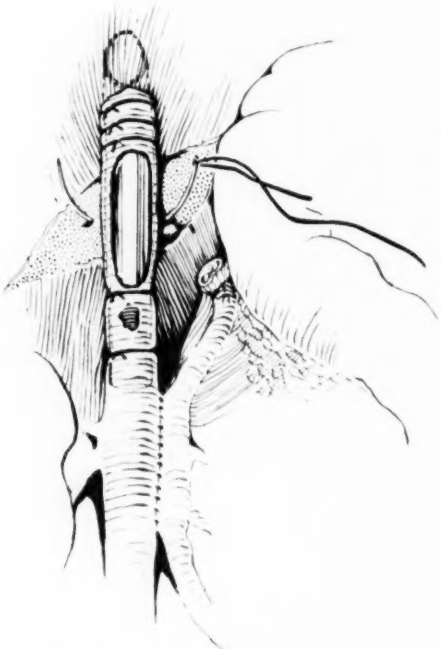

Fig. 6.—Several ligatures of fishing line have been placed around cava between liver and diaphragm. Liver has been excised, and cannula is being anchored to posterior trunk muscles by several interrupted sutures, preventing respiratory and emetic tugging on Eck fistula.

(that is, a clamp with longitudinal grooves) is placed above the ligatures, and the structures in the gastrohepatic omentum are severed. The clamp is left in situ to be removed with the liver. The coronary ligaments are now seized by a hemostatic forceps and carefully severed. Bleeding points in the diaphragm must be picked up with long forceps and coagulated or tied.

The right coronary ligament having been similarly severed, it is possible to insinuate the finger or a hemostatic forceps behind the cannula in such a manner as to pass a ligature around the upper extremity of the siliconed pyrex® glass cannula. Four or five ligatures of fishing line are then tied about the upper extremity of the cannula in such a manner that the movements of the diaphragm will not loosen the ligatures. Next, hepatic tissue is scraped from the inferior vena cava over the cannula by careful use of a knife or a tonsil dissector. The liver is then severed from the ventral face of the cannula by a bold sweep of the knife above and by the cautious use of the scissors below. Only the cava over the front of the cannula is removed with the liver. Possibly a few fragments of liver tissue remain behind and adjacent to the diaphragmatic ligatures, and these may be removed by thumb forceps and the careful use of scissors. Bleeding points are then carefully sought in each dome of the diaphragm. Three interrupted sutures are now passed about the cannula so that it is anchored in position to the posterior abdominal wall. In this way respiratory and emetic tugging of the diaphragm will not poke the lower end of the cannula against the Eck fistula. We believe that this last maneuver is of great importance in preventing postoperative oozing from the Eck fistula, an oozing which may not be visible to the surgeon after the hepatectomy but which may nevertheless be fatal, since a loss of 1 cc. of blood every five minutes can result in sufficient hemorrhage during the survival period to render the preparation unphysiological and almost useless for study. Finally, the pyloric segment of the stomach is anchored by one stitch to the abdominal wall. The abdominal incision is rapidly closed in three layers, careful attention being paid to hemostasis. If desirable, a cannula can be inserted into the external jugular vein to facilitate postoperative administration of glucose every hour.

## COMMENT

Liverless dogs so prepared require dextrose every hour in quantities which slowly increase from ¼ gm. per kilogram per hour. After a period which varies between 12 and 30 hours, the dextrose injections become ineffectual in restoring the animals to a normal condition; they become comatose and spastic, breathe peculiarly, go into convulsions, and die. During their life they become jaundiced, their urine becomes loaded with uric acid, and their protein catabolism breaks down, an extraordinarily rapid pulse develops, and they show a remarkable hemorrhagic tendency so that the incisions may bleed. If they live long enough, their blood clots poorly or fails to clot; they become anuric and then finally die. It is noteworthy[7] that their survival is facilitated by massive dosage with penicillin but that essentially the clinical picture is unchanged, being merely prolonged for a number of hours. Why these animals finally die in terms of mechanism is one of the mysteries of

7. Markowitz, J.; Lotto, W.; Lougheed, W.; Rappaport, A. M.; Archibald, J.; Downie, H. G., and Munroe, S.: Presented at the Toronto Physiological Society, January, 1952.

physiology. Bollman and Mann [8] have shown that transfusion of blood early in their careers increases their survival period. McMaster and Drury (1929) [9] have shown that a cross circulation of a liverless rabbit with a normal rabbit well on after hepatectomy does not increase its survival period. We are therefore ignorant of why an animal without a liver finally dies.

The technic described by us results in preparations which are vigorous and long-lived in 75% of cases. The operation is a feasible one if one bears in mind the pons asinorum of the method, the Eck fistula. If the experimenter can perform this with easy assurance, the operation is practical; otherwise, he would be better advised to dispose of the portal circulation by evisceration and to administer insulin and glucose during the survival period of the animal.

8. Bollman, J. L., and Mann, F. C.: Transaction Eighth Conference on Liver Injury, New York, Josiah Macy Jr. Foundation, 1949, p. 110.

9. McMaster, P. D., and Drury, D. R.: Proc. Soc. Exper. Biol. & Med. **27**:47, 1929.

# METHODS OF ALTERING THE INCIDENCE OF EXPERIMENTAL ULCERS IN DRAGSTEDT ANIMALS

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EXPERIMENTAL ulcers have been produced by many surgical and chemical methods. None has proved to be entirely satisfactory for the study of all phases of the ulcer problem in man. With the appearance of a large number of new antisecretory compounds, the need for an acute hypersecretion type of ulcer has developed.

Dragstedt and others [1] showed that when the antrum of the stomach was transplanted to the large intestine a marked increase in gastric secretion occurred and that in animals so prepared ulcers tended to develop. The ulcers thus produced were acute (perforation occurred in about three weeks), and they involved the jejunum opposite the gastric stoma. Dragstedt demonstrated that in 80% of the animals on which a gastrojejunostomy was done with antral transplants to the colon jejunal ulcers developed in about 3 to 4 weeks and some as early as 10 days (Fig. 1). When we duplicated this procedure in a series of 10 animals, 9 of the 10 animals died of perforated jejunal ulcers in 21 days.

In approximately 20% of Dragstedt's animals, ulcers developed in the duodenum if the antrum of the stomach was transplanted to the bowel in a peristaltic manner and a gastroduodenostomy was done (Fig. 2).

We varied Dragstedt's procedure by anastomosing the antral transplant to the large bowel in an antiperistaltic manner in a second series of 10 animals. In this series healthy mongrel dogs of both sexes, weighing 8 to 10 kg., were used. The animals were starved for 24 hours prior to surgery and were anesthetized with pentobarbital (veterinary nembutal® sodium [2]), which was administered intravenously in a dosage of 1 ml. per 2 kg. of body weight. The abdomen was shaved, prepared with mercocresols (tincture of mercresin) and draped with clean, nonsterile towels, as for a laparotomy. Clean, nonsterile instruments were used. Rubber gloves were worn by the operators.

After the abdomen was opened, the pylorus was transected and the duodenal stump was closed in two layers with a running silk suture. The junction of the

From the Research Department, The Upjohn Company.

1. Dragstedt, L. R.; Oberhelman, H. A., and Smith, C. A.: Experimental Hyperfunction of the Gastric Antrum with Ulcer Formation, Ann. Surg. **134**:332, 1951.

2. Veterinary nembutal® sodium contains, per cubic centimeter, 60 mg. of pentobarbital sodium, 10% alcohol, and 20% propylene glycol in water for injection.

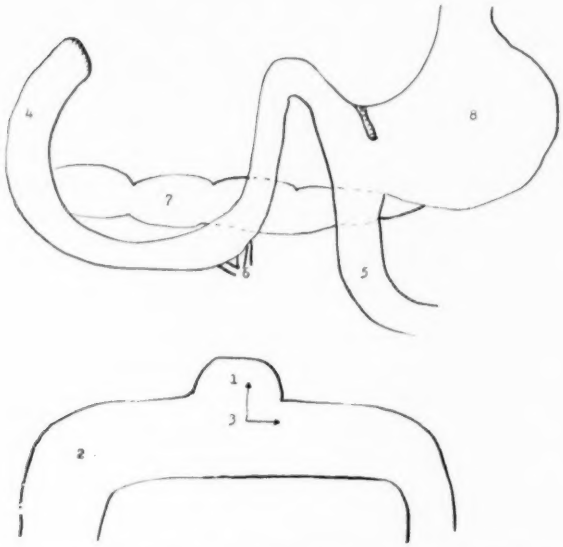


Fig. 1.—Gastrojejunostomy with antral transplant into colon in peristaltic manner, permitting fecal material to fill antrum. In 21 days jejunal ulcers developed in 9 of the 10 animals. *1*, antral transplant; *2*, colon; *3*, direction of peristalsis; *4*, duodenum; *5*, jejunum; *6*, ligament of Treitz; *7*, pancreas; *8*, stomach.

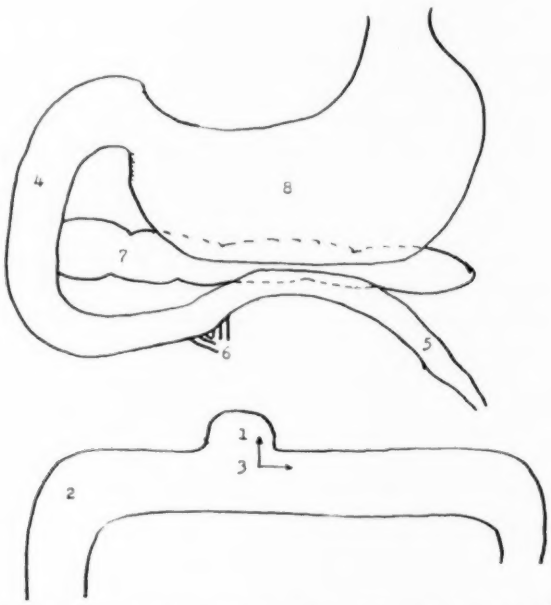


Fig. 2.—Gastroduodenostomy with antral transplant into colon in peristaltic manner, permitting fecal material to fill antrum. In 21 days duodenal ulcers developed in 20% of the animals.

antrum and the stomach was transected. A two-layer gastrojejunostomy was done, making the stoma of the stomach the same diameter as the lumen of the jejunum. After the distal end of the antrum was closed, the proximal end was anastomosed to the large bowel. This anastomosis was usually 5 to 6 in. (13 to 15 cm.) distal to the ileocecal junction. Open anastomoses were used throughout.

Postoperatively the animals were awakened with picrotoxin. The picrotoxin dosage, usually 1 to 2 ml., was sufficient to cause the animals to become restless but was not enough to produce convulsions. The animals received 200 to 300 ml. of isotonic sodium chloride subcutaneously in the neck and 500,000 units of penicillin the first day after surgery. They were kept on liquids for 24 hours and then given the regular laboratory diet. There were no surgical deaths in this series.

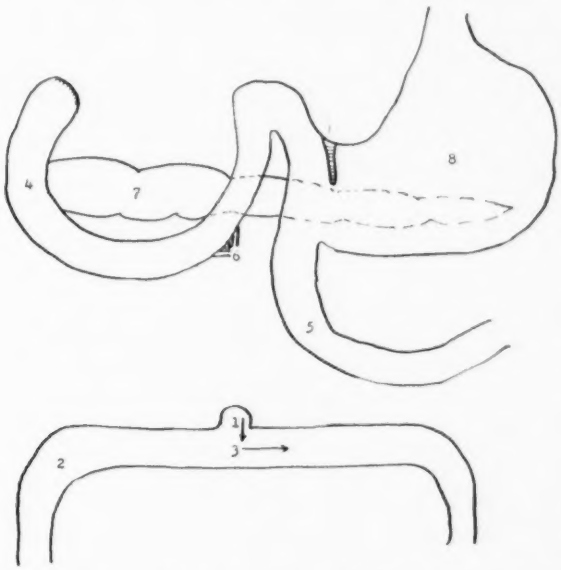


Fig. 3.—Gastrojejunostomy with antral transplant into colon in antiperistaltic manner, permitting fecal material to bypass antrum, thus allowing antrum to remain contracted and empty. In 24 to 70 days acute perforated ulcers developed in only 3 of the 10 animals. Of the remaining seven animals only three showed ulcers at autopsy at three months.

In the first animal in this group, an ulcer developed which perforated and caused its death in 24 days. Two other animals died from peritonitis secondary to perforated ulcers during the 10th week. The remaining seven animals were killed on the 90th day. Four of the seven had jejunal ulcers, and three had no ulcers (Fig. 3).

Autopsies on these animals showed that the antral transplants had contracted down and contained no fecal material, even though the contents of the bowel in some of the animals was watery. This contracture of the antrum due to the manner of anastomosis was the only observed variant in the two series.

From a comparison of the two series it would appear that the antrum of the stomach, when transplanted to produce ulcers of the acute type, must be placed

with the proximal end of the antrum anastomosed to the large bowel so that the fecal contents will enter and distend the antrum. In our first series, which was a duplication of Dragstedt's work, in 9 of the 10 animals jejunal ulcers developed in 21 days or less. This compares favorably with Dragstedt's series,[3] in which ulcers developed in 8 of the 10 animals in approximately three weeks.

In our series, in which the antrum was anastomosed in an antiperistaltic manner with the distal end connected to the colon, the antrum tended to remain empty and did not distend. This resulted in a delayed production of ulcers in a lower percentage of animals.

## CONCLUSION

In a comparison of two series of antral transplants in which the only variable was the manner of anastomosing the antrum to the colon, it appears that the presence of food or fecal material in the antrum is a necessary stimulus for gastric hypersecretion and ulcer production.

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# HEMANGIOMA OF CHEST WALL WITH EXTENSION INTO MEDIASTINUM AND EXTRADURAL SPACE

## Report of a Case

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HEMANGIOMAS occur in practically all visceral and somatic elements of the body and numerically are common tumors,[1] but when they occur in skeletal muscles, they are uncommon tumors, as evidenced by Watson and McCarthy's report of only 10 cases among 1,308 hemangiomas studied.[2] Shallow and co-workers collected 335 cases of hemangioma of skeletal muscles from the world literature up to 1944.[3] Of these, 39 involved the muscles of the thoracic wall; most of these tumors were small and involved only one muscle.

Elkin and Cooper reported 19 cases of large hemangiomas, 3 of which involved various muscles of the chest wall.[4] Two of these tumors were completely excised; the third, only partially because of its extent.

Dumbbell tumors of the mediastinum and spinal cord make up a small percentage of all spinal-cord tumors. The great majority of these have their origin in nerve tissue. Heuer studied 64 dumbbell tumors, 43% of which were nerve-tissue tumors. There were no hemangiomas in this group.[5]

This report concerns a patient recently treated at the University of Chicago Clinics for a very large cavernous hemangioma of the left thoracic wall, with extension into the posterior mediastinum and into the extradural space as a dumbbell or

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hourglass tumor. The extradural extension produced neurologic difficulties that were responsible for the patient's being seen.

REPORT OF CASE

A white woman, aged 52, was referred to the psychiatric clinic at Albert Merritt Billings Hospital by her family physician on June 7, 1949. Nineteen months prior to her first visit, she began to experience a burning sensation in her feet, which was noted at higher levels as time went on until it was felt throughout both lower extremities. She also complained that at the same time her legs began to feel heavy and tired. Three months prior to her first visit, she stated that her legs began to get "stiff," and this feeling progressed. During the month prior to entry the patient had noted involuntary flexion movements of both legs, more marked when she was lying down. Her difficulties had progressed to a point where walking was impossible, and she had become bedridden during the month prior to admission.

The patient had noted no loss of either bladder or rectal control.

The past history was not remarkable, except that the patient had been aware of the existence of a large soft mass in the area over and beneath the left scapula. She was not certain how long it had been there, although she recalled that it had been present in her late teens. She stated that this tumor had never caused symptoms, and she did not believe that it had grown at all for many years. Many years previously biopsy had been performed on the mass, but it bled profusely and the patient was told that it could not be removed but that it probably would never cause her any trouble, since it was a fatty tumor.

Examination revealed a middle-aged white woman who was unable to walk because of spastic paralysis of the lower extremities. There was a tumor of moderately soft consistency with very indistinct borders, measuring approximately 15 by 20 cm., lying over the lower two-thirds of the scapula and also extending medially and inferiorly to the scapula. It did not appear to be fixed to the skin but seemed to be firmly attached to the underlying chest-wall muscles and, to a less extent, the spinal musculature. The mass was nontender and the skin over it was normal in appearance. Pressure caused no change in the size. No thrill was palpable over it, and no bruits were heard. Neurologic examination revealed diminished to absent sensation up to about the fourth thoracic segment. There was marked weakness bilaterally of the lower extremities, as well as some weakness of the abdominal musculature. The knee jerks were graded 4+ bilaterally, and the ankle jerks 2+ with marked clonus. There were bilateral Babinski reflexes and absence of abdominal reflexes. The upper extremities were normal in all respects. The remainder of the physical examination was noncontributory.

The results of routine blood counts, urinalysis, and a serologic test on the blood and spinal fluid were all within normal limits. A spinal puncture revealed evidence of a partial block in the spinal canal.

An x-ray of the chest showed multiple small opacities in the soft tissues over most of the left hemithorax posterolaterally. There was rather marked bilateral hypertrophy of the second, third, fourth, and fifth ribs, with new bone formation along the inferior surfaces posteriorly. Erosion of the vertebral end of the left fourth rib and the bodies of the third and the fourth thoracic vertebra were demonstrable, along with destruction of the pedicles on the left. The foramen between the fourth and the fifth thoracic vertebra was markedly enlarged on the left. A rounded opacity was seen lying at the costovertebral junction in the posterior mediastinum on the left at about the level of the fourth rib.

The diagnosis of a tumor of the spinal cord was made. It was felt that it was probably a dumbbell type of tumor, inasmuch as a tumor mass could be seen in the posterior mediastinum, and that the most likely diagnosis was neurofibroma. The roentgenologist raised the question whether or not the tumor mass outside the chest wall was a hemangioma, because of the multiple calcification within it. At the time, however, it was not realized that the spinal-cord tumor was connected with the chest-wall tumor; therefore it was thought that the latter was merely coincidental, since it had been present for a great many years and had neither changed in size nor produced symptoms.

The patient was advised to have a laminectomy with removal of the intrathoracic portion of the tumor at the same operation, or, if this were not feasible, the intrathoracic portion could be removed later.

*First Operation.*—Accordingly, on June 14 a laminectomy from the second to the sixth thoracic vertebrae was carried out by Dr. Theodore Rasmussen. It was found that the laminae of the second, third, and fourth thoracic segments were eroded by a dark-purplish neoplasm. These laminae were completely fused and were very thin. The tumor extended from the superior border of the third thoracic vertebra to the inferior border of the fifth vertebra and filled the extradural space, except for about one-fourth of the space in the right anterior portion. The dura was opened to verify the fact that the tumor was entirely extradural. The tumor was found to extend into the thorax on the left between the fourth and fifth thoracic vertebrae, the stalk of which was over 2 cm. in diameter. The tumor was removed with considerable difficulty because of its marked vascularity. During its removal, at least two intercostal nerves on the left side had to be sacrificed. Because the operation had been lengthy and the blood loss considerable (3,500 cc. was transfused during surgery), it was thought inadvisable to continue with the intrathoracic portion of the operation.

The postoperative course was essentially uneventful. An indwelling catheter was required for a week, after which it was removed. The involuntary flexion movements of the lower extremities

Fig. 1.—Preoperative anteroposterior and lateral chest films. Note phleboliths lying in tissues in posterolateral chest wall. Hypertrophied ribs with new bone formation along the inferior borders are seen. Note mediastinal tumor, seen only on anteroposterior film.

ceased immediately, and the legs regained their strength slowly. Within several months the patient had improved to a point where she could get around in her house unassisted and could walk outside with the aid of a cane.

Gross Pathology: The specimen consisted of a bluish-gray, lobulated tumor mass measuring 4.5 by 2.5 by 20 cm. and weighing 11 gm. It cut with considerable resistance. About one-half of the tumor presented a fine honeycomb appearance, with the remainder composed of what appeared to be large thrombosed blood vessels.

Microscopic Pathology: The tissue was composed of a mass of vascular spaces of varying sizes. In some areas the spaces appeared very large and thin-walled. In other areas there were numerous smaller vascular spaces. These channels were separated by a loose cellular stroma of variable thickness that consisted of immaturely developed connective tissue.

*Second Operation.*—The patient was readmitted to the hospital in October, 1949, for removal of the chest-wall and intrathoracic portions of the tumor. Neurologic examination at this time

Fig. 2.—*A*, gross specimen from chest wall. *B*, low power photomicrograph of portion of tumor removed from extradural space; × 27.

showed marked improvement. The patient could walk unassisted, although her gait was somewhat awkward. The knee jerks were still 4+, but the ankle clonus had disappeared.

After it was determined that the tumor was a hemangioma, it was realized that the chest-wall tumor was not merely coincidental but was a hemangioma that had grown into the mediastinum and extradural space. There was no change in the size of the chest-wall tumor, and the chest x-ray was unchanged.

On Oct. 6, the patient was operated upon through a long incision over the approximate course of the left seventh rib. The skin was not involved by the tumor. The tumor mass appeared to consist of a large amount of fat in which there were numerous large blood spaces. The boundaries of the tumor were indistinct. It was found to infiltrate parts of the latissimus dorsi, the serratus anterior, the rhomboideus minor, the trapezius, and the erector spinae muscle mass. It also appeared to involve the posterior ends of the third and fourth ribs and a small amount of the intercostal muscles in this area. These rib segments were removed along with portions of the involved musculature. The main mass of the tumor was removed; however, complete extirpation was impossible owing to the indistinct borders and the extent of the tumor. The operation was again long and tedious because of the extreme vascularity of the tumor.

It was decided best to postpone the intrathoracic portion of the operation, since the procedure had been longer and blood loss greater than had been contemplated. Recovery from the operation was uneventful.

Gross Pathology: The specimen was a 650 gm. flat, rectangular, yellowish-red mass which measured 25 by 15 by 3 cm. Within the mass were portions of fat, muscle, and fascia. Many small (5 to 10 mm.) hard, smooth nodules (phleboliths) were palpable within the tissues. On section the mass was predominantly yellow, with portions of muscle and large, tortuous, blood-filled spaces.

Microscopic Pathology: Sections of this tumor were similar to those of the first one except that there was a large amount of fatty tissue present.

*Third Operation.*—The last stage of the operation was not accomplished until May 23, 1950, because of the patient's reluctance to submit to another operation. At this admission, she had regained somewhat more strength in her lower extremities and her gait was fairly good. The area from which the chest-wall tumor had been removed was well healed, and there was no functional impairment of the shoulder girdle. X-rays of the chest revealed no change in the mediastinal tumor; the previous shadows produced by the phleboliths were absent.

The chest was entered through the bed of the fifth rib. A firm encapsulated tumor mass approximately 5 cm. in diameter was found adherent to the costovertebral junction over the fourth and fifth ribs. It was easily removed with little bleeding, in contrast to the first two operations. Recovery from the operation was uneventful.

Since that time the neurologic signs have been stationary. There is still slight weakness of the legs, but the patient walks well without assistance. There is no evidence of any recurrence of the tumor.

Gross Pathology: The specimen was a firm tumor mass measuring 4 by 4 by 2 cm. and weighing 14 gm. When cut, the mass was found to contain many wide blood-filled sinuses. Some phleboliths were present.

Microscopic Pathology: The appearance was similar to that of the other two specimens.

## COMMENT

It seems most likely that this tumor arose in the muscles of the thorax and extended from them into the posterior mediastinum in the region of the third and fourth ribs posteriorly. From there it must have grown into the extradural space as a dumbbell tumor. The chest-wall portion was known to have been present for over 30 years and may have been present much longer. It is impossible to state how long the intrathoracic portion had been present, but it seems fair to surmise that the extradural extension was of less than two years' duration because of the patient's history.

This tumor, as is the case with many hemangiomas of muscle, was not circumscribed. The borders were indefinite, with a gradual fading away of the tumor into

normal muscle. By contrast, the other two parts were well encapsulated and well demarcated, although quite adherent to surrounding structures. The intrathoracic and extradural portions of the tumor had produced considerable erosion of bone, presumably by pressure. The rather striking bilateral hypertrophy and new bone formation of some of the upper ribs are interesting. Presumably, the greatly increased vascularity on the left side, where the tumor was situated, could cause the changes seen on that side. However, the changes on the right side were almost as striking, and the only portion of the tumor extending past the midline was a small part of the extradural tumor—this in spite of the fact that the patient's symptoms were of 19 months' duration and she had been completely unable to use her legs for several

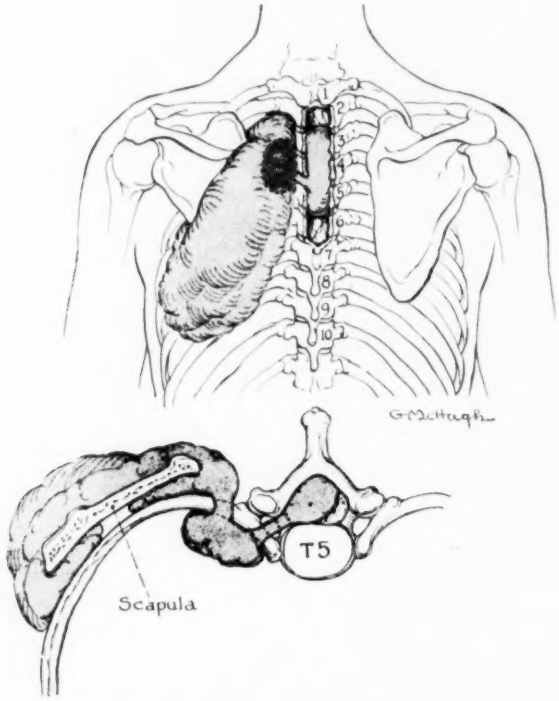


Fig. 3.—Diagrammatic representation of tumor.

weeks prior to the operation. Although parts of a number of muscles were excised from the chest, there was no functional impairment of the shoulder girdle.

## SUMMARY AND CONCLUSIONS

A case of a large hemangioma of the chest wall with extension and formation of a dumbbell tumor involving the middorsal cord, with spastic paralysis of the lower extremities, is presented.

Three operations were required to effect removal of the tumor. A small amount was left in the chest-wall muscles. Recovery from the paralysis of the lower extremities was marked but not complete.

# INFLUENCE OF HEPATIC ARTERY LIGATION ON REGENERATION OF LIVER TISSUE IN THE RAT

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WHEN DOGS or rats are subjected to partial hepatectomy at repeated intervals, the remaining liver increases in bulk to replace the deficit. If one-fifth to three-fourths of a dog's liver is removed, the remaining part regenerates completely in from six to eight weeks. Similarly a rat liver will resume its previous size in 14 to 16 days following partial removal. It often happens that the restored liver weighs more than the original organ. According to Markowitz,[1] the remaining part of the liver responds as rapidly and completely after the second or third partial hepatectomy as after the first.

The cause of hepatic restoration may possibly be the relatively increased blood supply, since after operation blood from the portal vein and the hepatic artery traverses a smaller mass of tissue. In a paper on the relation of portal blood flow to liver maintenance, Rous and Larimore [2] pointed out the effects on that organ of ligation of branches of the portal vein. There resulted a complete atrophy of the corresponding parenchyma, with an increase in the size of the remaining organ. The authors found that ligating a hepatic duct had the same effect in inducing atrophy as tying a branch of the portal vein.

Mann,[3] early in his research, found that if an Eck fistula had been made some time before removal of liver tissue hepatic regeneration did not occur after partial hepatectomy.

It has been reported by several authors and confirmed by our experience in the past that the main hepatic artery may be safely ligated in the dog and in the rat without producing any gross clinical or pathological changes in the animals. The purpose of the present experiment was to determine the effect, if any, of ligation of the hepatic artery, followed by or in combination with partial hepatectomy, as demonstrated in the regenerated liver tissue.

This work was aided in part by a grant from the United States Public Health Service.

From the Department of Surgery, Edward J. Meyer Memorial Hospital, and the University of Buffalo School of Medicine.

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## METHODS AND MATERIALS

One hundred twenty adult male white rats from Wistar stock, of similar age and weighing approximately 250 gm., were maintained on a stock diet, consisting of hydrogenated cottonseed oil (crisco®), cornstarch, lactalbumin, a salt mixture, brewers' yeast, and percomorph liver oil, in definite amounts. Daily dietary intake and body weights were recorded. Food was withheld for 24 hours prior to the removal of any liver tissue.

Inhalation ether anesthesia was used for all operative procedures and aseptic technique employed to prevent wound contamination. The main hepatic artery in the rat was isolated readily in the portal triad and a 00000 silk ligature placed around it to occlude the vessel completely. That this ligature completely eliminated arterial blood from all hepatic tissue was demonstrated with injection of a vital dye into the vascular system. This procedure consisted of exposing the hepatic artery and occluding the portal vein. Evans blue (T-1824) dye was injected continuously into the left ventricle. The heart continued to contract for three to four minutes. At death, blue discoloration of the liver, due to dye entering the patent hepatic artery, was noted. The procedure was repeated in another specimen, in which both the portal vein and the hepatic artery were occluded. No dye entered the liver. Partial hepatectomy was carried out with a modification of the classic method described by Higgins and Anderson.[4] A minimum of 50% of the liver was removed.

Liver tissue was examined for any chemical or structural changes with determinations of the following factors:

1. Total wet weight. The portion of the liver was rapidly removed, blotted on filter paper to remove as much blood as possible and quickly weighed on an analytical balance.

*Experimental Groups Studied*

| Group | Condition | Number of Specimens |
|---|---|---|
| I | Normal | 53 |
| II | Partial hepatectomy | 17 |
| III | Hepatic artery ligation | 29 |
| IV | Hepatic artery ligation plus simultaneous partial hepatectomy | 20 |
| V | Hepatic artery ligation for 30 days, then partial hepatectomy | 15 |
| VI | Hepatic artery ligation for 60 days, then partial hepatectomy | 10 |

2. Glycogen. Since the value for liver glycogen alters rapidly, the livers were immediately sampled for glycogen. These samples were dropped into tubes containing 40% KOH, and the tubes were then heated. Analyses were carried out according to the Good, Kramer, and Somogyi modification of Pfluger's method.[5]

3. Total lipid. Wet tissue samples were analyzed with the Fenn and Haege modification of the Kaplan and Chaikoff method.[6]

4. Protein. Wet tissue samples were analyzed with use of the Kjeldahl procedure and a conversion factor of 6.25.

5. Water content. To determine water content, tissue samples were dried to constant weight at 95 to 100 C.

6. Tissue. Sections of liver tissue were taken for microscopic examination and stained for fat and connective tissue.[7]

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The rats were separated into groups (I to VI) and the liver studied under the conditions shown in the Table. Specimens were examined 30 and 60 days after the operative procedure. The number of specimens in each group carried through the analytical procedures is also given.

## RESULTS

*Group I.*—All rats continued to gain weight at an equal rate during the course of the experiment; the average gain was 100 gm. Animals exhibiting any sign of infection or parasite infection of the liver (Cysticercus fasciolaris or ova of Capillaria hepatica) were eliminated from the study. Dietary requirements of all groups were

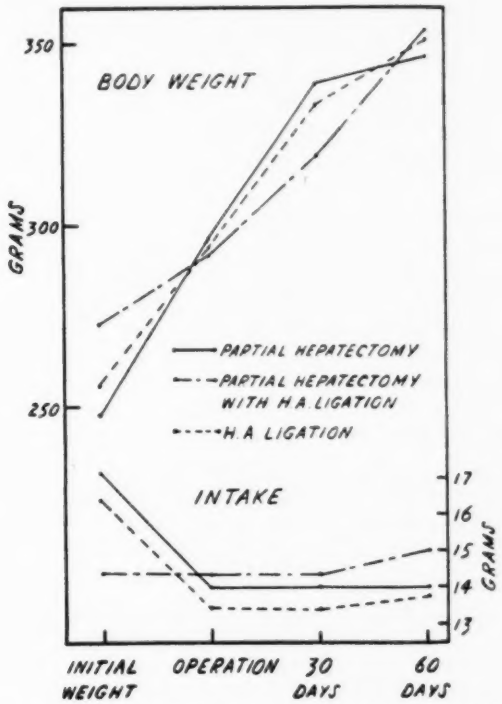


Chart 1.—Graphs showing similarity of body weight and dietary weight in all groups.

similar, though during the control period the daily intake was slightly higher for all rats. Chart 1 summarizes these data.

Early in the experiment it was noted that the liver glycogen values were persistently low, the average value in 53 normal livers being 0.11 gm. per 100 cc. All other analyses gave results within the usual range of normal values.

Maintaining rats on this particular diet for varying periods of time showed no measurable alteration in the liver tissue.

*Group II.*—In the determinations performed, regenerated liver tissue 30 and 60 days following partial removal showed quantitative values identical with those of normal liver tissue. On microscopic examination, however, there was noted an

increase in the stainable fat, which was diffuse throughout the liver after 30 days. This diminished in amount and became limited to the area of the central vein after 60 days.

*Group III.*—Following ligation of the hepatic artery, there were no gross chemical alterations other than an increase in the total nitrogen values after 60 days. This increase was slight but probably mathematically significant

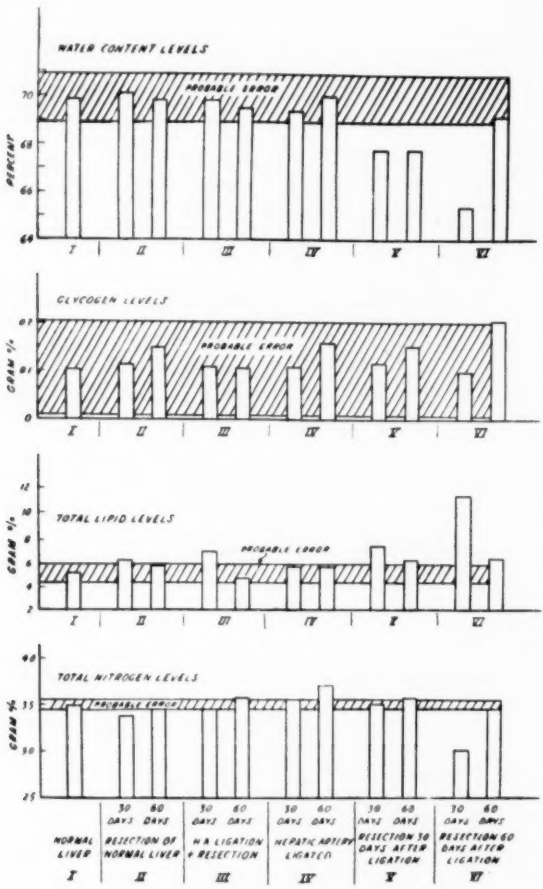


Chart 2.—Results of analyses for total nitrogen, total lipid, glycogen, and water content in the six experimental groups listed in Table.

*Group IV.*—Simultaneous ligation of the hepatic artery plus partial hepatectomy resulted in little change in the chemical picture. The total lipid values 30 days after operation showed what may be a statistically significant elevation, though this was not very striking. Once again microscopy revealed a marked increase in the stainable fat in the liver cells and, in addition, the presence of many vacuoles.

*Groups V and VI.*—When the main hepatic artery was ligated at an initial operation and partial hepatectomy performed at a subsequent time, either 30 or 60 days later, there was a marked alteration in the regenerated liver. The results appeared more marked in the group partially hepatectomized 60 days after ligation. There was not only a great increase in the stainable fat 30 days after partial removal of the liver but an actual elevation of the total lipid content. In these samples decreases in the total nitrogen- and water-content values, which were consistent with the rise in the lipid fraction, were also demonstrated. Once again the return toward or to normal was demonstrated 60 days following partial hepatectomy. In all experiments there were minor fluctuations in the liver-glycogen values but none differed significantly from those found for the control rats.

Chart 2 summarizes the results of analyses for total nitrogen, total lipid, glycogen, and water content for each group. The probable error graphed was computed for the 53 normal livers.

## COMMENT

Rats withstand ligation of the hepatic artery and maintain a fairly normal nutrition. Chemically there are few demonstrable differences from normal following ligation, except for slight elevation of the total-nitrogen levels of the liver. Perhaps this indicates an increase in fibrous tissue 60 days after operation, though in our study microscopic examination did not reveal confirmatory evidence. In addition, when ligation of the main hepatic artery is performed simultaneously with partial hepatectomy, the remaining portion undergoes the same degree of hyperplasia as does liver with intact arterial blood supply and in a similar manner. However, if the artery is ligated and partial hepatectomy performed at a subsequent time, then abnormal regeneration occurs. There are marked elevations in the total lipid levels and histologically true fatty changes in the liver cells. Evidently the time factor is important, since liver tissue which has functioned under decreased oxygenation for a period of weeks does not regenerate in a normal manner. It is difficult to explain the production of fatty livers 30 days after partial hepatectomy in rats previously prepared with ligations and the disappearance of that fat into either the biliary or the vascular systems. The process appears similar to that demonstrated in the liver with various deficiency diets. However, regeneration of arterial circulation through collateral channels over a period of weeks may be a factor in the later return to normal composition.

Another interesting finding in this experiment was the extremely low glycogen levels persistently maintained in these rats on this specific diet, with no other notable deviations from normal.

## SUMMARY AND CONCLUSIONS

Ligation of the main hepatic artery in the rat not only is compatible with survival but, combined with partial hepatectomy, does not alter liver regeneration or restitution to any great degree when the two procedures are carried out simultaneously.

With the hepatic artery ligated several weeks before the partial hepatectomy, there was a significant increase in the liver total lipid fraction 30 days after partial removal. However, this returned toward or to normal after a subsequent interval of 30 days.

Miss Sarah Camiolo, Mrs. Elva Wilkins, Mrs. Florence Drews, and Miss Mary L. McPherson gave technical assistance, and Mr. Harold C. Box made the statistical analysis.

# SYMPTOMS OF COMMON DUCT STONES

## Analysis of Clinical Data on One Hundred Sixty-Five Patients Having Explorations of the Common Duct

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STONES in the common bile duct as a cause of jaundice were described by Michael Ettmüller [1] 243 years ago. Exploration of the common duct was performed by Marcy, of England, (cited by Ochsner [2]) in 1882. The operation was introduced in Germany by Langenbach [3] and Kümmel [3] in 1884 and Knowsley-Thornton [3] performed the first successful operation five years later. In 1891 Charles McBurney (cited by Glenn [4]), before the New York Surgical Society, reported operating upon a patient who had been jaundiced for a long time and had lost 63 lb. (29 kg.) in weight. The common duct was approached through an incision in the duodenum, the ampulla of Vater divided, and the common duct split to remove a stone. The patient recovered and regained her health. In 1892 Robert Abbe (cited by Glenn [4]) reported that he had operated upon four patients and removed common duct stones from each. He opened the common duct, removed the stones, drained the duct with a small rubber tube, and closed the duct with fine silk.

In the past 60 years much has been learned about jaundice and other biliary tract diseases. The detection of common duct stones, however, rests with the operating surgeon, despite the information obtained from laboratory examinations or x-ray studies. His idea is to remove all common duct stones, meanwhile avoiding unnecessary negative explorations. His judgment as to when a common duct should or should not be explored is based upon the history and the clinical, laboratory, and operative findings.

Are there specific symptoms or findings in those cases in which stones are found in the common duct that do not exist in cases in which common duct exploration does not reveal stones? We have reviewed the clinical data on 165 consecutive patients having common duct explorations performed at the time of primary cho-

From the Departments of Surgery, St. Luke's Hospital, and the University of Illinois College of Medicine.

1. Ettmüller, M.: De ictero flavo, albo et nigro, cited by Waters, W., and Snell, A. M.: Diseases of the Gallbladder and Bile Ducts, Philadelphia, W. B. Saunders Company, 1940, p. 6; cited by Graham, E. A.; Cole, W. H.; Copher, G. H., and Moore, S.: Diseases of the Gallbladder and Bile Ducts, Philadelphia, Lea & Febiger, 1928, p. 143.

2. Ochsner, A. J.: Surgical Diagnosis and Treatment, Philadelphia, Lea & Febiger, 1921, Vol. 2, p. 419.

3. Cited by Ochsner.[2]

4. Glenn, F.: Exploration of the Common Bile Duct, Ann. Surg. **112**:64-79 (July) 1940.

5. Footnote deleted.

lecystectomy at St. Luke's Hospital in an effort to answer this question. In this study, stones were found in 87 patients, or 53%. In 78 patients, or 47%, no stones were found in the common duct (Table 1).

TABLE 1.—*Findings in 165 Common Duct Explorations.*

| Findings | Cases | |
|---|---|---|
| | No. | Per Cent |
| Stones found | 87 | 53 |
| Stones not found | 78 | 47 |

INCIDENCE OF COMMON DUCT STONES

The average incidence of exploration of the common duct in 25,807 operations for cholecystitis was 23% [6] and the incidence of common duct stones found at the time of operation varied between 4.2 and 36.8%, with an average incidence of 11.3%.

While doing 1,000 routine autopsies, Crump [7] found biliary duct stones in 24% of 325 patients with chronic cholecystitis with stones. His study, however, included

6. (*a*) Clute, H.: Common Duct Stones, J. A. M. A. **95**:1568-1571 (Nov. 22) 1930. (*b*) Cheever, D.: Methods and Results in the Surgical Treatment of Diseases of the Biliary Passages, New England J. Med. **213**:463-470 (Sept. 5) 1935. (*c*) Lahey, F., and Swinton, N.: Stones in the Common and Hepatic Duct, ibid. **213**:1275-1280 (Dec. 26) 1935. (*d*) Eliason, E., and Erb, W.: Mortality in Surgery of Biliary Tract, Ann. Surg. **101**:460-468 (Jan.) 1935. (*e*) Carter, R. F.; Greene, C. H., and Twiss, J. P.: Diagnosis and Treatment of Diseases of Biliary Tract, Philadelphia, Lea & Febiger, 1939, Chap. 32. (*f*) Walters, W.; Gray, H. K., and Priestley, J. T.: Report of the Surgery of the Gallbladder, Liver, and Pancreas for 1937 and 1938, Proc. Staff Meet., Mayo Clin. **14**:773-782 (Dec. 6) 1939. (*g*) Evans, C. A., and Everts, E. L.: A Review of 645 Operations on the Gallbladder and Bile Ducts, Wisconsin M. J. **38**:529-532 (July) 1939. (*h*) Allen, A. W., and Wallace, R. H.: The Surgical Management of Stone in the Common Bile Duct, Ann. Surg. **111**:838-847 (May) 1940. (*i*) Glenn,[4] (*j*) Zollinger, R.: The Surgical Treatment of Gallbladder Disease, Rev. Gastroenterol. **7**:420-429 (Sept.-Oct.) 1940. (*k*) Walters, W.; Gray, H. K., and Priestley, J. T.: Lesions of Biliary Tract for 1940, Proc. Staff Meet., Mayo Clin. **16**:681-688 (Oct. 22) 1941. (*l*) Goldman, L., and Bell, H. G.: Surgical Management of Disease of the Gallbladder, J. A. M. A. **117**:1582-1585 (Nov. 8) 1941. (*m*) Walters, W.; Gray, H. K.; Priestley, J. T., and Counseller, V. S.: Lesions of Biliary Tract for 1941, Proc. Staff Meet., Mayo Clin. **17**:545-550 (Nov. 4) 1942. (*n*) Gans, H.: Choledocholithiasis: A Clinical Study of 109 Patients Operated Upon, Am. J. Surg. **56**:423-431 (May) 1942. (*o*) O'Shea, M.: Stones in Ductus Choledochus, ibid. **57**:279-283 (Aug.) 1942. (*p*) Hooker, D.: Exploration of the Common Bile Duct: Review of 165 Cases, ibid. **60**:88-95 (April) 1943. (*q*) Clagett, O. T.; Counseller, V. S., and Waugh, J. M.: Report of Biliary Surgery for 1942, 1943 and 1944, Proc. Staff Meet., Mayo Clin. **21**:5-10 (Jan. 9) 1946. (*r*) Adams, R., and Stranahan, A.: Cholecystitis and Cholelithiasis: An Analytical Report of 1104 Operative Cases, Surg., Gynec. & Obst. **85**:776-784 (Dec.) 1947. (*s*) Walters, W.; Gray, H. K.; Priestley, J. T., and Waugh, J. M.: Annual Report on Surgery of the Biliary System and Pancreas, Proc. Staff Meet., Mayo Clin. **23**:615-622 (Dec. 22) 1948. (*t*) Mahorner, H.: Combined Supraduodenal and Transduodenal Exploration of the Common Bile Duct, Ann. Surg. **129**:766-773 (June) 1949. (*u*) Edye, B. T.: Surgery of Common Bile Duct, M. J. Australia **2**:347-349 (Sept. 3) 1949. (*v*) Smith, C. H.; Walther, C. D.; Maunz, D. H.; McCutcheon, S. A., and Medden, E. J.: Biliary Tract Surgery in a Small Community Hospital: A Ten-Year Survey, Ann. Surg. **132**:1086-1092 (Dec.) 1950.

7. Crump, C.: Incidence of Gall Stones and Gall-Bladder Disease, Surg., Gynec. & Obst. **53**:447-455 (Oct.) 1931.

cystic duct stones. He gave no statistics on common duct stones alone. Clute [6a] found common duct stones in 8.4% of 619 patients on whom cholecystectomy had been performed between the years 1910 and 1926. In his second report, of 413 cases, from 1927 to 1930, he explored the common duct approximately twice as often and found approximately twice as many stones as in the first series.

Allen and Wallace [6h] reviewed the cases from the Baker Memorial and the Massachusetts General Hospital in 1940. In their personal series of 266 biliary tract

TABLE 2.—*Incidence of Common Duct Stones*

| Author | Date | Total No. of Cases | % of Common Ducts Explored | % of Explored Common Ducts with Stones | % of Total No. of Cases with Common Duct Stones |
|---|---|---|---|---|---|
| Clute, H. M.[6a] | 1910-1926 | 619 | 15.5 | 54.2 | 8.4 |
| | 1927-1930 | 413 | 33.8 | 42.8 | 17.9 |
| Cheever, D.[6b] | 1935 | 426 | 37.9 | 44.3 | 16.4 |
| Lahey, F. H., and Swinton, N.[6c] | 1930-1935 | 733 | 40.3 | 45.6 | 18.4 |
| Eliason, E. L., and Erb, W.[6d] | 1935 | 529 | 17.4 | 58.5 | 10.2 |
| Carter, R. F.; Greene, C. H., and Twiss, J. P.[6e] | 1939 | 3,306 | 7.8 | 81.9 | 6.4 |
| Walters, W.; Gray, H. K., and Priestley, J. T.[6f] | 1939 | 930 | 18.7 | 44.8 | 8.3 |
| Evans, C., and Everts, E. L.[6g] | 1939 | 645 | 19.6 | 49.6 | 9.7 |
| Allen, A. W., and Wallace, R. H.[6h] * | 1940 | 266 | 59.7 | 61.6 | 36.8 |
| | .... | 2,088 | 37.1 | 44.4 | 16.4 |
| Glenn, F.[6i] | 1940 | 907 | 12.1 | 59.8 | 6.6 |
| Zollinger, R.[6j] | 1940 | 442 | 37.8 | 46.6 | 17.7 |
| Walters, W.; Gray, H. K., and Priestley, J. T.[6k] | 1941 | 1,079 | 24.0 | 58.7 | 13.8 |
| Goldman, L., and Bell, H. G.[6l] | 1941 | 435 | 19.8 | 54.6 | 10.9 |
| Walters, W.; Gray, H. K.; Priestley, J. T., and Counseller, V. S.[6m] | 1942 | 1,012 | 22.8 | 56.2 | 12.8 |
| Gans, H.[6n] | 1942 | 586 | 18.7 | 48.6 | 9.0 |
| O'Shea, M.[6o] | 1942 | 1,438 | 6.4 | 82.8 | 5.3 |
| Hooker, D.[6p] | 1943 | 2,117 | 7.8 | 53.3 | 4.2 |
| Clagett, O. T.; Counseller, V. S., and Waugh, J. M.[6q] | 1942 | 1,059 | 25.5 | 57.5 | 14.7 |
| | 1943 | 1,121 | 25.1 | 49.1 | 12.3 |
| | 1944 | 1,335 | 24.7 | 46.5 | 11.5 |
| Adams, R., and Stranahan, A.[6r] | 1947 | 1,104 | 45.7 | 36.9 | 16.8 |
| Walters, W.; Gray, H. K.; Priestley, J. T., and Waugh, J. M.[6s] | 1948 | 1,172 | 23.6 | 42.6 | 10.8 |
| Mahorner, H.[6t] | 1949 | 78 | 28.2 | 63.6 | 17.9 |
| Edye, B. T.[6u] | 1949 | 719 | 63.7 | 28.8 | 18.3 |
| Smith, C. H.; Walther, C. D.; Maunz, D. H.; McCutcheon, S. A., and Medden, E. J.[6v] | 1950 | 348 | 36.0 | 37.0 | 13.0 |
| Strohl, E. L.; Diffenbaugh, W. G., and Guynn, V. | 1951 | 900 | 18.3 | 53.0 | 9.6 |
| Totals and average | | 25,807 | 23.0 | 48.6 | 11.3 |

* Personal and Massachusetts General Hospital Series.

operations, 36.8% of the patients had stones in the common duct; however, in the entire hospital series of 2,088 biliary tract operations, stones were found in the common duct in 16.4%. Allen and Wallace state that the difference between their personal series and the hospital series may be accounted for on the basis of the type of patients entering the general hospital clinic in comparison with the selected group of private patients.

In the annual reports from the Mayo Clinic,[8] it is noted that explorations of the common duct at the time of cholecystectomy were made more frequently—from

8. Walters, Gray, and Priestley.[6f,k] Walters, Gray, Priestley and Counseller.[6m] Clagett, Counseller, and Waugh.[6q] Walters, Gray, Priestley and Waugh.[6s]

18.7% in 1939, to 23.6% in 1948—with the result that more common duct stones were found.

AGE

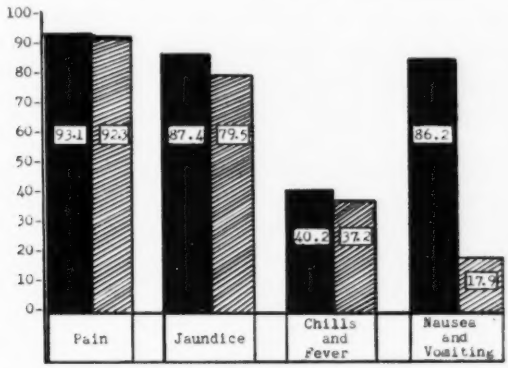
The ages of the patients ranged between 21 and 84 years. Thirty-seven common ducts were explored in patients in the fifth decade, 57 in patients in the sixth decade, and 33 in patients in the seventh decade. Thus, in the fifth, sixth, and seventh decades there were 127 common duct explorations, or 76.9% of the total series. Stones were found in the common duct in 47.8% of those patients explored who

TABLE 3.—*Age Incidence*

| | 20-29 Yr. | 30-39 Yr. | 40-49 Yr. | 50-59 Yr. | 60-69 Yr. | Over 70 |
|---|---|---|---|---|---|---|
| Stones found in common duct | 5 | 6 | 19 | 27 | 21 | 9 |
| No stones found in common duct | 6 | 8 | 18 | 30 | 12 | 4 |
| Total explorations of common duct | 11 | 14 | 37 | 57 | 33 | 13 |

TABLE 4.—*Sex Distribution*

| Sex | 20-29 Yr. | 30-39 Yr. | 40-49 Yr. | 50-59 Yr. | 60-69 Yr. | Over 70 | Total |
|---|---|---|---|---|---|---|---|
| Male | 1 | 3 | 15 | 21 | 15 | 6 | 61 |
| Female | 10 | 11 | 22 | 36 | 18 | 7 | 104 |




Symptoms in 165 cases in which common duct was explored. Black columns indicate per cent of cases in which stones were found; hatched columns, per cent of cases in which stones were not found.

were under 60 years of age. In patients past 60 years of age on whom explorations were performed, the incidence of common duct stones increased to 65.2%.

SEX

In this series of 165 patients, 104, or 63.04%, were women, and 61, or 36.96%, were men. Of the group between 20 and 40 years of age, there were 21 women and 4 men who had common duct explorations. During the child-bearing years there is an increase in the incidence of cholecystic disease in women.

*Pain.*—Pain, the most frequent complaint, was present in 93.1% of those patients in whom stones were found and in 92.3% of those patients in whom no stones were found (chart). The duration of symptoms is of importance. A preponderance of the patients who had common duct stones gave a history of attacks of pain over a period of years. In most instances the pain was located in the epigastrium when stones were found in the common duct.

*Jaundice.*—Intermittent, existing, or a history of jaundice was present in 87.4% of those patients in whom common duct stones were found and in 79.5% of patients in whom stones were not found.

*Chills and Fever.*—Chills and fever were present in 40.2% of patients in whom stones were found and in 37.2% of the patients in whom exploratory findings were negative.

*Nausea and Vomiting.*—Nausea and vomiting were present in 86.20% of patients in whom common duct stones were found, and these symptoms were also present in 17.9% of patients in whom stones were not found. The history of nausea and vomiting was of shorter duration in the latter group.

## COMMENT

The classic symptoms of pain, jaundice, chills and fever, and nausea and vomiting are considered indicative of common duct stones. One to all of these symptoms may be absent. Trueman,[9] in a review of 219 cases of common duct stones from the Mayo Clinic, found no pain recorded in 22.3%, no jaundice in 39.3%, and no chills and fever in 65.8%.

In our study, pain, dating back months or years, was a characteristic symptom in those patients in whom stones were found in the common duct. The type of pain is important. It is usually located in the epigastrium when stones are present in the common duct. Zollinger[10] showed experimentally that distention of the cystic or the common duct produced severe epigastric pain. Furthermore, he demonstrated that distention of the gall bladder produced less severe right upper quadrant pain. Severe pain suggests cystic duct or common duct obstruction with distention.

A history of jaundice or existing jaundice is not positive evidence of common duct stones. Intermittent, existing, or a history of jaundice was present in 79.5% of the cases in which stones were not found in the common duct. Inflammation about the cystic and common ducts may cause pressure and edema, with subsequent jaundice.

Chills and fever are due to infection within the biliary ducts, and such infection may be present in patients with or without stones in the common duct. In our study, these symptoms were present in 40.2 and 37.2% of the patients, respectively.

Nausea and vomiting were the symptoms most helpful in differentiating patients with common duct stones from those without common duct stones. Nausea and vomiting were present in 86.2% of patients with stones, in contrast to 17.9% of

9. Trueman, K. R.: Symptoms of Common Duct Stones: Review of 219 Cases, Proc. Staff Meet., Mayo Clin. **15**:283-285 (May 1) 1940.

10. Zollinger, R.: Observations Following Distension of the Gallbladder and Common Duct in Man, Proc. Soc. Exper. Biol. & Med. **30**:1260-1261 (May) 1933; Significance of Pain and Vomiting in Cholelithiasis, J. A. M. A. **105**:1647-1652 (Nov. 23) 1935.

patients without stones. In 1928, Schrager and Ivy [11] demonstrated in dogs that pronounced vomiting followed distention of the cystic duct in 87% of the animals. When an obstruction was placed in the ampulla of Vater, pronounced vomiting occurred in 91% of the dogs. In 1933, Zollinger [10] showed experimentally that in humans distention of the common duct is always followed by pronounced nausea and vomiting. He recommended that the common duct be explored in all cases in which there are significant nausea and vomiting. He stated that exploration is indicated when these symptoms are present, irrespective of the size of the common duct or of a history negative for jaundice.

Indications for exploration of the common bile duct in this series of 165 patients were the following: (1) palpation of common duct stone; (2) dilatation or thickening of the common duct; (3) small stones in the gall bladder with a patent cystic duct; (4) abnormal bile, with sediment, upon aspiration of the common duct; (5) existing, intermittent, or a history of jaundice; (6) evidence of cholangitis, and (7) thickening of the head of the pancreas, or evidence of chronic pancreatitis. As a result of our study, we believe that the following symptoms should be added indications for exploration of the common duct at the time of gall-bladder surgery: (8) pronounced nausea and vomiting, and (9) epigastric pain.

Cholangiography at the time of operation was not done in this series of cases. Cholangiograms are made routinely before removal of a common duct tube.

## SUMMARY AND CONCLUSIONS

In a series of 165 consecutive common duct explorations at the time of cholecystectomy at St. Luke's Hospital, Chicago, common duct stones were found in 87 patients, or 53%. This represents an incidence of 9.66% common duct stones in 900 operations for cholecystitis. The incidence of common duct explorations in the 900 operations was 18.3%.

Common duct stones were found with greater frequency in patients over 60 years of age who had common duct explorations.

Pain was the most frequent complaint. It was present with almost equal frequency in the patients with and in those without stones in the common duct. The pain was located in the epigastrium in most instances when stones were found in the common duct.

The history of jaundice or its presence is not certain evidence of common duct stones.

Nausea and vomiting were prominent symptoms in patients in whom common duct stones were found. These symptoms were present in 86.20% of those patients in whom common duct stones were found and in 17.9% of those patients without stones in the common duct.

It is our opinion that the symptoms of epigastric pain, and nausea and vomiting should be added to the commonly accepted indications for exploration of the common bile duct.

122 S. Michigan Ave.

11. Schrager, V. L., and Ivy, A. C.: Symptoms Produced by Distension of Gallbladder and Biliary Ducts, Surg., Gynec. & Obst. **47**:1-13 (July) 1928.

# DEFECTS IN RIGHT DIAPHRAGM OF INFANTS AND CHILDREN WITH HERNIATION OF LIVER

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AND
JACOB C. HANDELSMAN, M.D.
BALTIMORE

HEMISPHERICAL bulging of a portion of the right diaphragm into the thorax has been revealed roentgenologically in children in a significant number of cases. In the isolated instances in which this type of abnormality has been reported previously,[1] it has usually been described as an eventration. The use of this term has done little to aid in the understanding of the clinical significance of this abnormality. A large group of cases in which the abnormality has ordinarily been described as an eventration is that in which diaphragmatic elevation has occurred secondary to phrenic palsy. Other allusions to eventration refer to the extremely rare situation in which one side of the diaphragm is entirely replaced by a thin membrane containing no muscle. If, however, one considers such a transformation as affecting only a portion of the diaphragm, with bulging upward of the membrane, the condition is anatomically indistinguishable from a congenital diaphragmatic hernia with a sac. The present attitude regarding surgical treatment of diaphragmatic hernia with or without a sac is sufficiently definite to establish the point that other diaphragmatic defects, clinically indistinguishable from them and subject to the same complications, must also be operated upon.

This report describes a group of similar abnormalities of the right diaphragm in five children. The abnormality in these cases consists in an attenuation of a section of the diaphragm which is normally muscular. The defect is central, circular, well-defined, and ringed by normal diaphragmatic muscle. In these patients the defect varies in extent from the area of half the right diaphragm to areas as small as 4 cm. in diameter. With decrease in its area, the lesion takes on increasing similarity to a true diaphragmatic hernia in that the surrounding normal phrenic muscle acts as a ring and the thinned-out membrane encompassed by it bulges into the thorax under abdominal pressure, as does a hernia sac. Ordinarily classified

From the Department of Surgery of The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital.

1. (*a*) Haeberlin, P.: Eine seltene Zwerchfellmissbildung (partielle einseitige Doppelbildung), Schweiz. med. Wchnschr. **23**:516, 1945. (*b*) Wolfson, S. A., and Goldman, A.: Strangulating Diaphragmatic Hernia of the Liver: Report of Case with Surgical Cure, Surgery **24**: 846, 1948. (*c*) Bradley, J. E., and Greiner, D. J.: Diaphragmatic Hernia, Am. J. Dis. Child. **66**:143, 1943. (*d*) Wagner, A.: Four Cases of Diaphragmatic Intumescence, Acta radiol. **26**:239, 1945.

as neither hernias nor what is implied by "eventration," these cases merit consideration as clinical entities in which the diagnosis can be made easily if the lesion is suspected. Appropriate therapy may be easily and successfully extended.

## REPORT OF CASES

CASE 1.—R. S., a Negro boy, was first admitted to the Harriet Lane Home of The Johns Hopkins Hospital on April 13, 1944, when he was 3 months old. He had been ill for four weeks with an acute pneumonic episode in the lower lobe of the right lung which had responded to sulfonamide therapy after five days of treatment. After clinical improvement, the infant was left

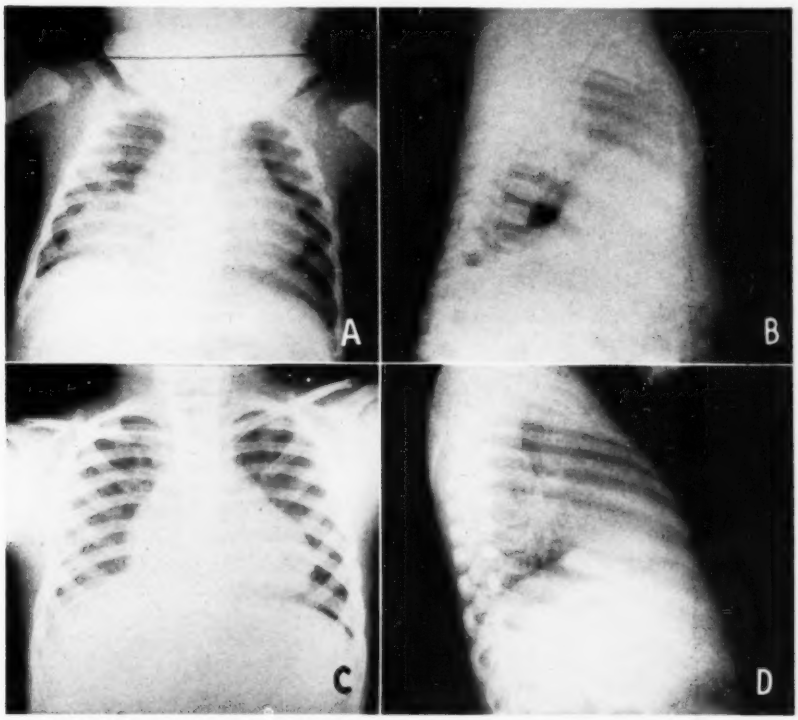


Fig. 1 (Case 1).—R. S., an 11-month-old Negro boy, was first admitted for pneumonia of lower lobe of the right lung. When this had cleared, the sharp, dense, rounded shadow (*A* and *B*) was noted, appearing to rise from the mediastinum or the diaphragm. At operation, a circumscribed fibrous defect of the right diaphragm was found, with liver bulging into it. After operative repair (*C* and *D*), the diaphragmatic outline and movement became and remained normal.

with a persistent nonproductive cough, occasional vomiting, and a dense shadow which could be seen on fluoroscopy, apparently above the diaphragm, anteriorly and medially on the right and left, crossing the mediastinal shadow. The gastrointestinal tract appeared to be in normal position, and it was felt by some observers that the mass was distinct from the diaphragm. Aspiration of the mass was unsuccessful. The child improved and was discharged.

He was followed in the outpatient department, with frequent roentgenographic and fluoroscopic studies. The peculiar shadow persisted, and exploratory thoracotomy was decided upon

in the thought that an operable tumor might be present. Although it was felt that the mass did not move with the diaphragm, the diagnosis of eventration was seriously entertained.

On Nov. 2, 1944, operation was performed by Dr. Blalock, with use of cyclopropane anesthesia. The chest was entered through a right anterolateral incision in the fifth interspace. The dome of the diaphragm was seen to be high, and its muscle appeared atrophic. An opening was made in the diaphragm, and liver alone was found to underlie the elevated portion. Biopsy was performed on a portion of the diaphragm. The incision in the diaphragm was closed by imbrication to reduce the arch of the dome of the diaphragm. Two rows of nonabsorbable surgical (silk) sutures were used. The lung was reexpanded and the chest wound closed in layers with silk. Examination of the excised tissue revealed that it contained no muscle but that it had collagen bundles which showed no scarring. It was felt that the collagen might have come from the normally tendinous portion of the diaphragm.

The postoperative course was marred only by an episode of otitis media necessitating myringotomy. X-ray studies revealed the displacement of the diaphragm to have been largely corrected. The patient was discharged 19 days postoperatively.

The child was followed in the outpatient department for three years, and his diaphragm continued to appear normal. In 1947, an umbilical hernia was repaired without event.

*Summary.*—Surgical correction of a membranous defect involving half of the right diaphragm was carried out in a 10-month-old child. The liver, bulging into the chest through the defect, had been mistaken for a mediastinal tumor. A persistent nonproductive cough was present preoperatively but has not recurred since.

CASE 2.—I. N., a white boy, was first seen in the Harriet Lane Home of The Johns Hopkins Hospital on Jan. 23, 1946, when he was 11 months old. The child had had a cough for six months, perspired excessively, and failed to gain weight satisfactorily. The cough had been present since an attack of pertussis at the age of 6 months. The family history was interesting only in that two spontaneous miscarriages preceded the pregnancy which produced the patient.

The infant appeared ill-nourished and poorly developed. There was suppression of breath sounds at the base of the right lung and in the right axilla. Fluoroscopy revealed the right diaphragm to be elevated, although its motion was considered to be within normal limits. In the roentgenogram an area of increased density extending from the lower portion of the right hilus toward the periphery was seen. It was felt that the child might be suffering from some chronic pulmonary disease, but bronchoscopy and bronchography failed to show any abnormalities. Subacute ethmoiditis was treated with radon and with penicillin nose drops, and the patient was discharged on Feb. 21.

After an acute upper respiratory infection, the patient was readmitted on June 6, with an exacerbation of his old trouble. Fluoroscopy and a roentgenogram taken at this time again revealed a high right diaphragm and areas of infiltration in the lower lobe of each lung. A bronchogram again showed no abnormality. It was suspected that an eventration or diaphragmatic hernia might account for these findings.

Operation was performed (M. M. R.) on July 7, 1946, with the patient under cyclopropane anesthesia. An incision was made posterolaterally through the right eighth interspace. The entire right half of the diaphragm was elevated, but only the lateral half contracted with respirations. Grossly, the two halves were indistinguishable except for this. A strip of diaphragm was taken for biopsy to include both portions. The medial portion of the diaphragm was then plicated anteroposteriorly onto the lateral, moving, portion, with two rows of interrupted silk sutures. The contour of the diaphragm was essentially normal at the end of this procedure, but its excursion seemed limited. The lung was reexpanded and the chest closed in layers with silk. The excised strip of diaphragm showed normal striated muscle throughout.

The child's postoperative course was not remarkable. X-ray study of the chest July 19 showed some tenting of the right side of the diaphragm. The patient was discharged on July 22.

The child has been seen on six occasions since operation. Three months postoperatively his diaphragm was normal on x-ray examination. He has been well and has gained weight slowly.

Despite recurrent upper respiratory infections, he has had no further difficulty with cough and no evidence of bronchopulmonary infection.

*Summary.*—A defect involving the medial half of the right diaphragm in a 17-month-old white boy was corrected surgically. A chronic nonproductive cough present for six months prior to operation has not recurred.

CASE 3.—D. J., a Negro boy, was first admitted to The Johns Hopkins Hospital on June 25, 1946, at the age of 2 years. He had been well except for an attack of diphtheria. While convalescing from this at the Sydenham Hospital, Baltimore, one month prior to admission, x-ray study of the chest demonstrated a bulging of the midportion of the right diaphragm, suggestive of eventration or herniation.

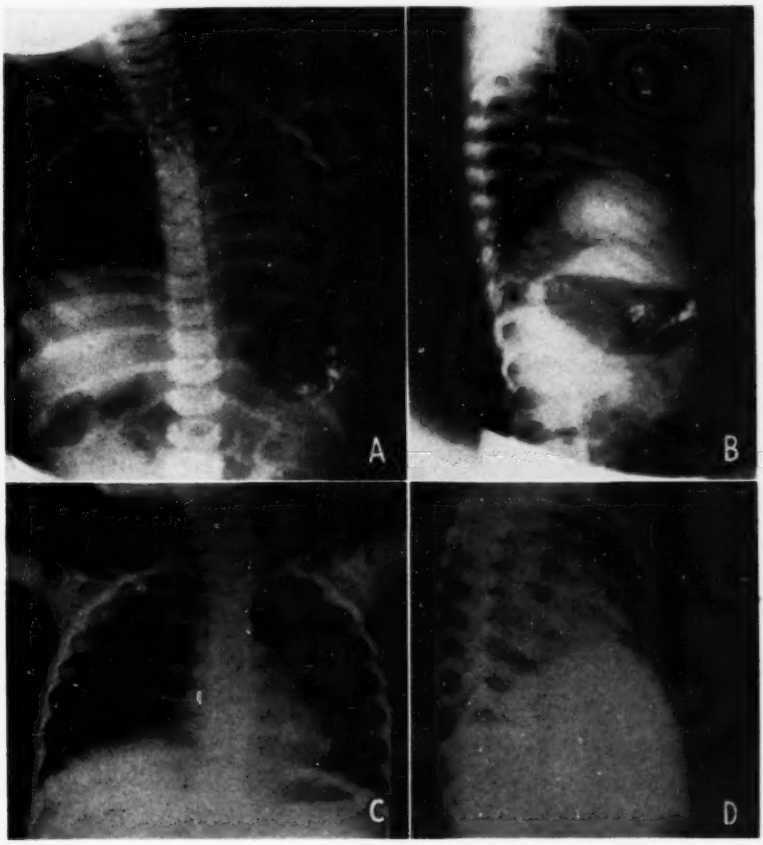


Fig. 2 (Case 2).—I. N., a 17-month-old white boy, had a history of repeated pulmonary infection with infiltration at the base of the right lung. Preoperative roentgenograms (*A* and *B*) show fairly uniform elevation of right diaphragm. The lateral view is characteristic of reported cases. After operation (*C* and *D*), the right diaphragm in posteroanterior films is seen to be less than one interspace higher than the left, instead of more than two interspaces. In the lateral view, the diaphragm is seen to be largely below the heart rather than overlapping it. Pulmonary infections did not recur.

Physical examination was remarkable only in that the diaphragm was found to descend poorly on the right. A roentgenogram made on June 27, was read as showing an unusual elevation of the midportion of the right side of the diaphragm. It was felt that this was a localized diaphragmatic defect.

With the use of cyclopropane anesthesia, operation was performed (M. M. R.) on July 7. The chest was entered through an intercostal incision in the eighth interspace. In the center of the right leaf of the diaphragm there were two bulging circular areas, each at least 4 cm. in diameter, gray and thin. A strip of one of these areas was taken for section. Liver lay beneath. A two-layer closure of the edges of the well-defined rings was carried out. The diaphragm appeared flat after this and seemed to contract well. The lung was reinflated, and the chest was closed. The excised tissue showed "scarring in diaphragmatic muscle."

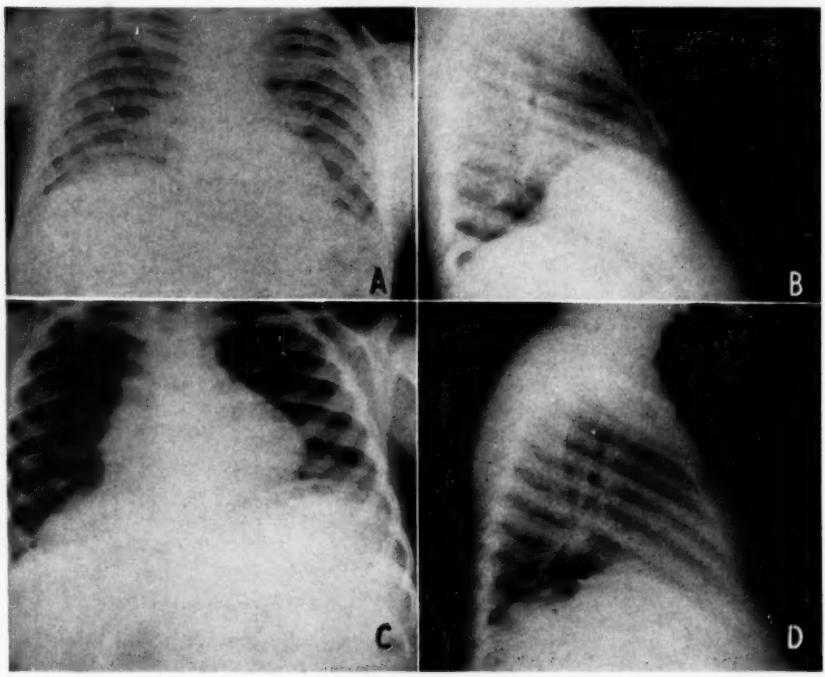


Fig. 3 (Case 3).—D. J., 2-year-old Negro boy, had typical preoperative roentgenograms (*A* and *B*), with postoperative restitution to normal (*C* and *D*) with, perhaps, some overcorrection. Two circular defects were present in the right diaphragm.

The child's postoperative course was unremarkable.

The child was next seen in the outpatient department on Sept. 23, at which time fluoroscopy showed the right diaphragm to be slightly tented but to contract well. One year later the contour of the right diaphragm was still somewhat irregular, but it moved well.

*Summary.*—Two small areas of eventration through the dome of the right diaphragm were repaired surgically in a Negro boy aged 2 years. The lesions were asymptomatic and had been discovered on routine chest x-ray. The sacs were filled with liver.

CASE 4.—B. G., a white boy, was first admitted to The Johns Hopkins Hospital on April 8, 1948, at the age of 12 days. He had been born at full term after a normal pregnancy and no known birth trauma. From the second day of life onward, he had episodes of cyanosis while feeding or crying. Fluoroscopy performed when the baby was 10 days old showed a mass in the right

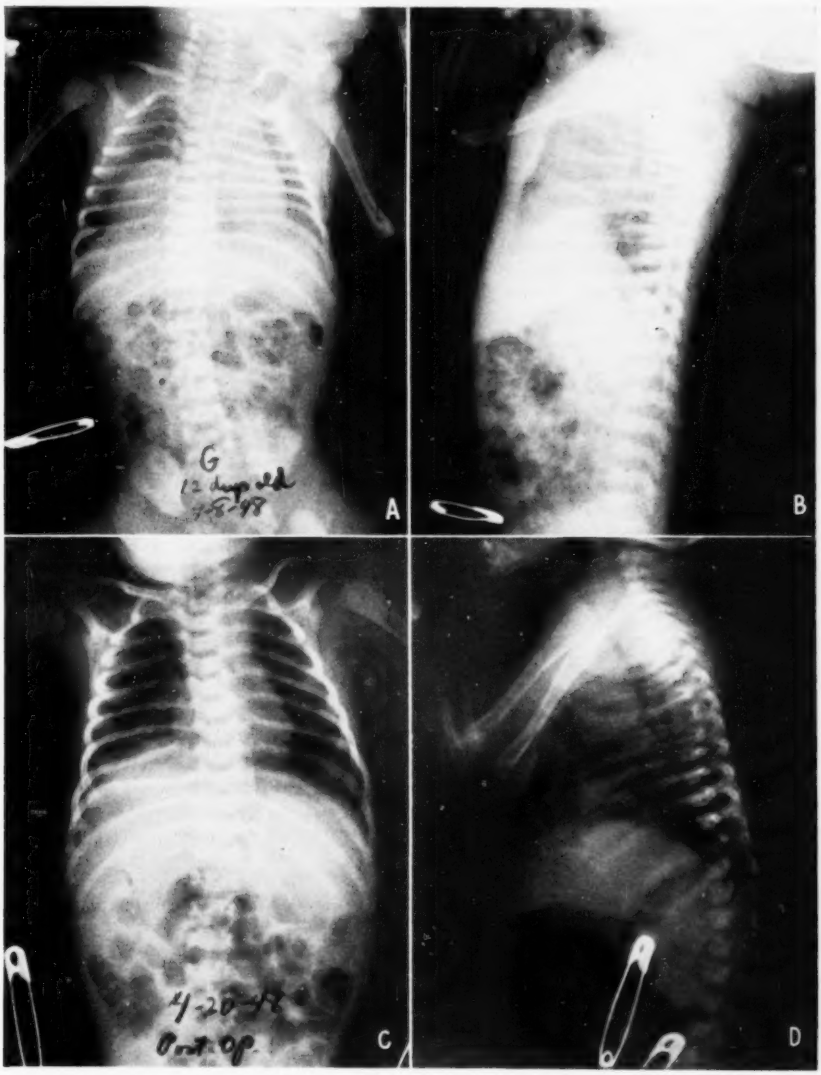


Fig. 4 (Case 4).—B. J., a 3-week-old white boy, had spells of cyanosis and apnea. The remarkable height to which the liver rose through the membranous defect is well shown in the posteroanterior roentgenogram (*A*) and less well in the lateral view (*B*). At the time of operation, the liver was seen literally to bump against the heart with each expiration. Postoperatively (*C* and *D*) diaphragmatic contour was restored, and the infant's difficulties lessened and disappeared. However, the patient shows evidence of retardation, and the degree to which the diaphragmatic lesion may have been responsible for his symptoms is not clear.

chest, which moved with the diaphragm. A roentgenogram showed the mass to lie anteriorly against the mediastinum and apparently to originate from the diaphragm. It was felt that this was most likely a diaphragmatic hernia.

The child appeared grossly normal but had frequent episodes of apnea and cyanosis, especially while crying. Neurological examination revealed no abnormality. Laryngoscopy and repeated fluoroscopy with barium swallows revealed nothing further, except that barium did not enter the mass. Operation was decided upon, with a tentative diagnosis of diaphragmatic abnormality permitting herniation of liver into the right chest.

Operation was performed (M. M. R.) on April 16, with the patient under ether anesthesia. A posterolateral incision through the eighth interspace on the right revealed a localized eventration of a portion of the right diaphragm in its anterior portion adjacent to the mediastinum. At this site, a thin blue-gray membranous portion of the diaphragm bulged upward from a base formed by the normal diaphragm. The ring was about 3 to 4 cm. in diameter. The "sac" was palpated and seemed to include only liver. With each expiration, the mass impinged on the right side of the apex of the heart. The bulging diaphragm and herniated liver were inverted into the abdomen and the margins of the ring brought together with a double layer of Lembert sutures. The lung was expanded and the chest closed.

The patient's postoperative course was unremarkable, but he continued to have intermittent episodes of cyanosis. However, these were less frequent and shorter and occurred only with crying and never with feeding. It was felt by the pediatricians that these were most likely due to breath holding. The child was discharged on the seventh day after operation.

When seen two weeks later, the child's episodes of cyanosis were even less frequent, and the father was pleased with his son's improvement. Six months later the child was again seen. His respiratory difficulty had cleared completely, and he was a powerful, fat baby. However, his development was definitely retarded, his skull was flat on the left, and he had left strabismus and right torticollis. It remained moot as to whether his mental respiratory difficulty was due to the diaphragmatic abnormality or a cerebral lesion.

*Summary.*—Repair of a localized eventration with protrusion of liver through the right diaphragm was carried out in a 3-week-old infant. Preoperatively he had had frequent episodes of apnea and cyanosis. These diminished in frequency postoperatively and had disappeared completely before the child was 6 months old. Manifestations of a cerebral lesion by this time, however, obscured the cause of his original respiratory distress.

CASE 5.—A Negro boy was admitted to The Johns Hopkins Hospital on March 10, 1950, when he was 11 months of age. Four months prior to admission he had had an episode of vomiting and diarrhea for three days. In the course of his treatment, a routine chest x-ray was made, and a smooth curved 4 by 8 cm. mass was seen in the right pericardiophrenic angle, blending with the mediastinum and diaphragm.

Physical examination on admission revealed no abnormalities, except for a small umbilical hernia. Repeated x-ray and fluoroscopic examinations were made in an effort to ascertain the movement of the mass relative to the diaphragm. It was felt that it did not move with the diaphragm. While a pericardial cyst could not be ruled out, it was held most likely that the lesion was a partial eventration with liver herniation.

On March 16, operation was performed (J. C. H.) with the patient under ether anesthesia. An anterolateral incision was made through the fourth interspace. In the right pericardiophrenic angle there was an outpouching of the diaphragm with a knob-like projection measuring 3 by 4 cm. at its base and protruding 6 to 8 cm. into the chest. The pouch, which appeared grossly like thinned-out diaphragm, was opened and found to be occupied by a "knob" of normal-appearing liver. The liver was readily replaced, a portion of the "sac" excised for examination, and the edges of the defect were approximated with a row of mattress sutures reinforced by a second row of interrupted sutures. The lung was reinflated and the chest wall closed. The specimen revealed histologically normal diaphragmatic muscle.

The child's postoperative course was unremarkable, and he was discharged nine days later. The diaphragm has remained normal on x-ray and fluoroscopic examination.

*Summary.*—Surgical repair of a localized defect in the right half of the diaphragm of an 11-month-old Negro boy was carried out. Liver had protruded through the defect, but the child was asymptomatic. The lesion was discovered incidentally during a fluoroscopic examination.

## COMMENT

The necessity for early surgical correction of congenital diaphragmatic hernias is generally recognized. The dangers associated with these lesions do not admit of procrastination. The integrity of any abdominal organ displaced into the thorax is jeopardized equally without regard to the lesion permitting the herniation. Thus, in a lesion of the left diaphragm, similar to those described above in the right diaphragm, precisely the same complications occurred as are seen in the more usual congenital diaphragmatic hernias. In this instance, an infant with a small defect in the left diaphragm suffered peritonitis from strangulation and perforation of a portion of stomach protruding into the fibrous sac. The case cited by Haeberlin further illustrates this point.[1a]

Herniation through the right leaf of the diaphragm has not been generally regarded as being equally fraught with danger because of the broad buttress provided by the right lobe of the liver. However, protrusion of the liver itself through the defect, as in the cases presented in this report, may produce its own symptoms so far as respiratory embarrassment or liver necrosis goes. Wolfson and Goldman in 1948 reported a child in whom a 2 in. (5 cm.) mass protruding through the diaphragm in the right phrenicopericardial sulcus proved to be strangulated liver.[1b] Bradley and Greiner, in 1943, cited an autopsy on a 7-week-old infant which reveals the extent to which herniation may occur.[1c] The child succumbed to respiratory insufficiency following protrusion of almost all of the right lobe of the liver into the thorax through a 4 cm. defect. The hazards seem sufficiently grave to warrant early operation in every case, whether the condition preoperatively is designated a hernia or a "partial" eventration.

In three of the five cases presented above, an initial complaint which was present disappeared or was altered after operation. Patients R. S. (Case 1) and I. N. (Case 2) had troublesome coughs which did not recur after surgical repair of the diaphragm. In B. J. G. (Case 4) episodes of apnea and cyanosis were the presenting complaint. These gradually subsided postoperatively, but the subsequent development of a picture highly suggestive of a congenital cerebral defect or injury has made it difficult to evaluate the role of the diaphragmatic abnormality.

As with other "survey" lesions of the chest, the uncertainty of differential diagnosis further influences one toward the decision to operate. Wagner in 1945 demonstrated the near-impossibility of distinguishing roentgenologically between this lesion (which he termed "liver hernia") and pericardial lipoma, congenital short esophagus, or subdiaphragmatic cyst.[1d] While a barium swallow would exclude the esophageal disorder, pneumothorax or pneumoperitoneum would eliminate the other possibilities.[2] The morbidity associated with these procedures per se would tend to discourage their use, particularly in the face of the equal applicability of transthoracic operation to all the lesions under consideration.

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2. Clay, R. C., and Hanlon, C. R.: Pneumoperitoneum in the Differential Diagnosis of Diaphragmatic Hernia, J. Thoracic Surg. **21**:57, 1951.

The operative procedure in itself has presented no difficulty. An incision through the fourth or fifth interspace anterolaterally or in the eighth interspace posterolaterally has offered ample exposure. The "sac" overlying the intruding liver is opened and the incision carried through the phrenic ring, if necessary. Reduction of the liver has been accomplished without difficulty. The excess attenuated membrane is inverted and the defect plicated in the direction of the incision. Usually, a closure with a layer of mattress sutures has been made, this suture line being then inverted under a layer of interrupted inverting sutures.

In four cases of this group, biopsy of the sac was carried out. In one instance fibrous tissue histologically indistinguishable from the tendinous portion of the diaphragm was obtained. In the remaining three instances, "muscle" or "scarred muscle" was found. While the condition is thus differentiated from a true hernia sac, the finding of diaphragmatic muscle in a thinned-out bulge of the diaphragm leads one to conjecture that the underlying pathological condition may be a localized affection of diaphragmatic innervation.

Convalescence from the surgical procedure has been uneventful in every instance. Clinically and roentgenologically the correction in each case has been complete and maintained.

## SUMMARY

Eventration of the diaphragm may involve a portion, rather than the whole, of the leaf of a diaphragm. As the involved portion becomes smaller, the resemblance to a congenital diaphragmatic hernia increases. The normal muscle of the diaphragm surrounding the affected area acts as a ring, permitting the thin atonic membrane of diaphragm to bulge into the thorax as a sac.

Five cases are presented in which this abnormality occurred in the right diaphragm of children. In three patients there appeared to be associated symptoms.

This abnormality should be considered in the differential diagnosis of masses low in the right chest that are roentgenologically sharply demarcated superiorly and not separable from the diaphragm inferiorly.

Surgical correction is safely and readily carried out transthoracically.

Operation is the recommended treatment in all cases, for the same reasons that it is indicated in the usual cases of diaphragmatic hernia.

# MANAGEMENT OF PAROXYSMAL HYPERTENSION FOLLOWING INJURIES TO CERVICAL AND UPPER THORACIC SEGMENTS OF THE SPINAL CORD

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AND
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PATHOLOGIC autonomic reflex mechanisms which accompany injuries to the cervical and upper thoracic segments of the spinal cord have been observed and described and their clinical manifestations studied by means of physiologic investigations during the period following the first and second world wars.[1] Many pathophysiologic phenomena were explained; yet no therapeutic effort was reported to eliminate permanently the most dangerous of these, namely, paroxysmal hypertension, which is caused by distention of hollow viscera and which threatens the life of the patient. The present study was stimulated by a previous observation [2] on three cases in which pathologic autonomic reflexes became suppressed after the subarachnoid injection of absolute alcohol administered in order to abolish skeletal spasticity.[3] Since subarachnoid alcohol block interrupts both afferent and efferent

Dr. John H. McGirr assisted in evaluating the patients.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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*Summary of Data on Seven Patients Undergoing Rhizotomy*

| Name | | L. W. | T. A. | C. O. | A. S. | C. S. | P. V. | H. J. |
|---|---|---|---|---|---|---|---|---|
| Level | | C-5 | C-6 L & T-1 R | C-5 | C-6 | C-6 L & C-7 R | C-7 | T-2 |
| Age, Yr. | | 31 | 31 | 22 | 40 | 28 | 22 | 25 |
| Level of rhizotomy | | T-9 | T-10 | T-10 | T-10 | T-11 | T-11 | T-11 |
| Time interval between injury and rhizotomy | | 15 mo. | 57 mo. | 23 mo. | 16 mo. | 15 mo. | 18 mo. | 56 mo. |
| Time interval after rhizotomy | | 9 mo. | 22 mo. | 2 mo. | 2 mo. | 19 mo. | 7 mo. | 16 mo. |
| Blood pressure without manipulation | Before | Irregular—high | Irregular—high | Irregular—high | Irregular—high | Irregular—high | Irregular—high | Irregular—high |
| | After | Regular—normal | Regular—normal | Regular—normal | Regular—normal | Regular—normal | Regular—normal | Regular—normal |
| Headache | Before | Severe | Severe | Severe | Severe | Severe | Severe | Severe |
| | After | Absent | Mild (rare) | Absent | Mild (rare) | Absent | Absent | Mild (rare) |
| Blood pressure with physiologic bladder distention | Before | 200/115 | 220/100 | 145/110 | 170/110 | 160/110 | 200/120 | 160/100 |
| | After | 116/70 (500 cc.) | 120/80 (1 hr. 180 cc.) | 84/50 (150 cc.) | 122/84 (245 cc.) | 120/78 (300 cc.) | 142/80 (500 cc.) | 155/80 |
| Blood pressure with artificial bladder distention | Before | 170/110 (150 cc.) | ? | 160/100 (100 cc.) | 132/86 (500 cc.) | 114/88 (300 cc.) | ? | 186/98 |
| | After | 120/78 (400 cc.) | 170/110 (125 cc.) | 130/84 (100 cc.) | 184/104 (400 cc.) | 180/90 (175 cc.) | 142/80 (400 cc.) | 170/105 (150 cc.) |
| | | | | | 100/62 (340 cc.) | 120/72 (225 cc.) | | delay cystogram |
| Perspiration | Before | Profuse | Profuse | Profuse | Profuse | Profuse | Profuse | Profuse |
| | After | "Just damp" | Mild | Mild | "Gets warm" | None | None | Profuse |
| Cutis anserina | Before | Present | Present | Present | Present | Present | Present | Present |
| | After | Unchanged | Unchanged | Mild | Less frequent | Absent | Absent (occurring with bladder not bowel distention) | Unchanged |
| Erection | Before | Present | Present | Present | Present | Present | Present | Present |
| | After | Present 50% 2 mo. postoperative | Present 100% 18 mo. postoperative | Absent | Absent | Absent | Absent | Present 75% 2 mo. postoperative |
| Spasticity | Before | Mild | Moderate (left) | Severe | Severe | Mild | Severe | Severe |
| | After | Mild | Mild (disappeared, left; present, right foot) | Mild (50%) | Moderate | None | Severe (after short interval of relaxation) | Mild (only abdominal) |
| Patella reflex | Before | Present | Present | Present | Present | Present | Present | Present |
| | After | Absent | Absent | Absent | Absent | Absent | Present (unilateral) | Absent |
| Achilles reflex | Before | Present | Present | Present | Present | Present | Present | Present |
| | After | Absent | Absent | Absent | Absent | Absent | Present (unilateral) | Absent |
| Babinski reflex | Before | Present | Present | Present | Present | Present | Present | Present |
| | After | Absent | Absent | Absent | Absent | Absent | Present (unilateral) | Absent |
| Bulbocavernosus reflex | Before | Present | Present | Present | Present | Present | Present | Present |
| | After | Absent | Present | Present (quickly exhausted) | Absent | Absent | Present | Present |
| Bladder function | Before | Cystostomy | Cystostomy | Cystostomy | Indwelling catheter | Cystostomy | Cystostomy | Indwelling catheter |
| | After | Unchanged | Unchanged | Unchanged | Indwelling catheter (first voiding since injury with poor balance) | Cystostomy (disappearance of vesicoureteral reflux) | Cystostomy (improved tone, first appearance of uninhibited waves) | Indwelling catheter (temporary good balance following pudendal nerve anesthesia) |

pathways below the level of injection, posterior rhizotomy at segments which supply the highly reflexogenic areas of the genitalia, bladder, and rectum would be a more logical therapeutic procedure. If it were proved that elimination of stimuli along the afferent pathways alone suffices to abolish paroxysmal hypertension, such a method then would be superior to alcohol injection by leaving the motor roots intact.

The present investigations were devised to study this problem in two ways: first, by attempting to interrupt noxious stimuli with reversible, topical, or conduction anesthesia, and, second, by analyzing the effect of posterior rhizotomy performed on seven patients with paroxysmal hypertension.

## MATERIAL AND PROCEDURE

These studies were made on seven patients who were later subjected to rhizotomy and on an additional number of patients who did not undergo this operation. The ages of the seven patients (Table) ranged from 22 to 40 years, and all had traumatic transsecting lesions in the lower half of the cervical or uppermost thoracic spinal cord, which rendered them essentially completely paraplegic; the patients of the untreated group had cervical lesions. All were severely handicapped by paroxysmal hypertension, particularly when they were subjected to urological instrumentation or even when catheters were changed. Similar observations were made on all patients before and after operation.

Preoperatively, serial observations were made on blood pressure, sweating, cutis anserina, and subjective symptoms such as headache and a feeling of faintness before, during, and after a variety of cutaneous and deep stimuli. Such stimuli included pinprick to various areas of the skin, pinching to the glans penis and testicles, anal manipulation with the examining finger, urethral distention either by the instillation of saline solution or by means of a Foley bag placed in the anterior urethra, and direct distention of the catheterized bladder with saline solution. In the latter instance, cystometric pressures were routinely recorded. The same observations were again recorded immediately after appropriate infiltration, block, or topical anesthesia with 1% procaine hydrochloride, intracaine® (β-diethylaminoethyl-*p*-ethoxy benzoate hydrochloride) or tetracaine hydrochloride (pontocaine® hydrochloride) solutions. The blood pressure was recorded at 1 to 2 minute intervals.

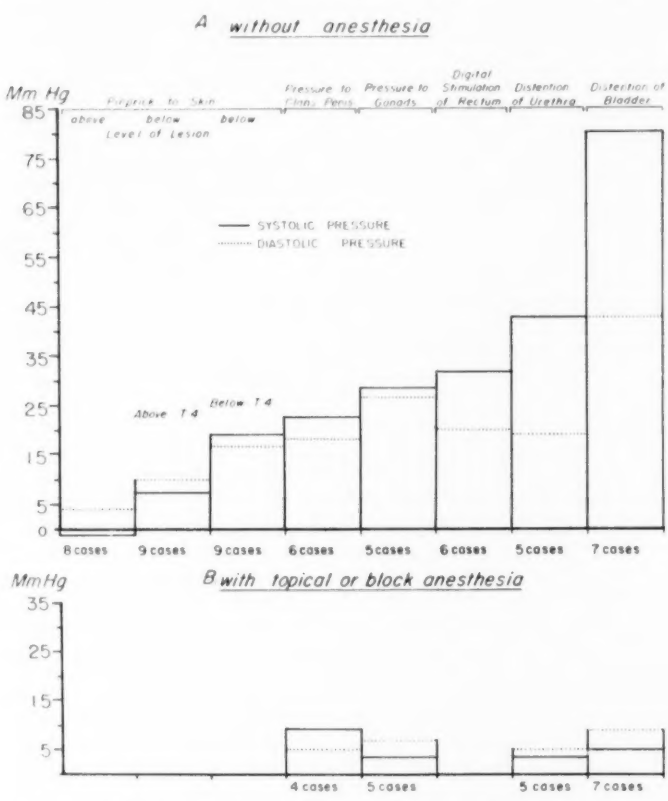
After sufficient data had been accumulated, operation was performed with the patient under sodium pentothal® anesthesia. The 11th and 12th thoracic laminae were usually removed, although frequently the 1st lumbar and part of the 10th thoracic arches were also revised. Blood pressure readings were made in each case before and after manipulation of the root and before its division between silver clips was accomplished. In one case the 11th and 12th roots were stimulated bilaterally (1.5 to 3 volts, 60 per second alternating pulses) with a Hinsey-Geohegan machine and the effect on blood pressure noted. The root sections progressed rostrocaudally in four cases and caudorostrally in one. In two instances, the division of roots was accomplished from above caudally on one side and from below cephalically on the other. All patients recovered without complications from the operation.

Observations were made at various times up to 23 months postoperatively in the same way as those described above, which were made preoperatively. In all cases described the period since operation is at least 2 months and the longest period is 23 months.

## RESULTS

*A. Effect of Stimuli from Various Parts of the Body on Blood Pressure and the Inhibiting Role of Anesthesia (Chart).*—Simple pinprick did not cause a rise of blood pressure when applied to the skin above the level of anesthesia (nine patients) but did so when applied below. The lower the skin segments stimulated, the higher rose the blood pressure until it reached a maximum from the segments which supply the genitoanal area.

The average rise was less marked (19 mm.Hg systolic, 17 mm.Hg diastolic—hereinafter reported systolic/diastolic mm.Hg, e. g., 19/17 mm.Hg) when the stimulus was applied below the fourth thoracic segment but above the genitoanal segments, and even smaller elevations (7/10 mm.Hg) occurred when it was applied between the fourth thoracic segment and the level of the lesion. After the skin was anesthetized either by local infiltration (two patients, 12th thoracic dermatome) or by block anesthesia (two patients, 2d and 3d sacral dermatomes) with 1%




Average values of blood pressure rise from cutaneous and visceral stimuli.

procaine hydrochloride solution, no elevation of blood pressure was noted on subsequent stimulation of the respective dermatomes.

Squeezing the tip of the glans penis (six patients), as done in testing the bulbocavernosus reflex, was accompanied by a rise of blood pressure (average elevation above the base line 23/17 mm.Hg). This rise could be reduced or completely eliminated by bilateral pudendal nerve anesthesia or by conduction anesthesia through the second and third sacral foramina (two patients in each category). Anesthesia of the dorsal nerve of the penis reduced the rise of blood pressure following pinprick to the glans penis in one patient, but conduction anesthesia at the

second and third sacral segments was without such effect in another patient. The latter observation was ascribed to a faulty technique of anesthesia.

Rectal stimulation by digital examination (six patients) caused an average rise of 32/21 mm.Hg, with a systolic range from 17 to 75 and a diastolic range from 8 to 45 mm.Hg above the base line. This rise could be increased when the finger was moved in the rectum.

Stimulation from pressure to the testis (five patients) resulted in an average rise of 27/26 mm.Hg, with a systolic range varying from 18 to 42 mm.Hg above the base line and a diastolic range from 15 to 40 mm.Hg. When conduction anesthesia with 1% procaine hydrochloride solution was applied to the ileohypogastric, ileoinguinal, and internal spermatic nerves, the average elevation was reduced to 4/8 mm.Hg, with an individual variation of 4 to 9 systolic and from 0 to 15 diastolic. By this procedure, therefore, pressure elevation after such stimulation was reduced an average of 23 mm.Hg systolic and 18 mm.Hg diastolic.

Distention of the urethra (5 patients) caused an average rise of 42/20 mm.Hg, with a systolic range from 20 to 87 and a diastolic from 10 to 36 mm.Hg. Topical anesthesia with 1% tetracaine hydrochloride solution reduced the average rise to 4/5 mm.Hg, while the individual elevations ranged from 8 to 28 systolic and from 0 to 18 diastolic. Therefore, topical anesthesia effectively reduced elevation of blood pressure from urethral distention by an average of 38 mm.Hg systolic and 15 mm.Hg diastolic.

Distention of the bladder (7 patients) caused a blood-pressure elevation averaging 78/41 mm.Hg, with a systolic range from 32 to 140 mm.Hg and a diastolic range from 25 to 63 mm.Hg. Topical anesthesia by the instillation of 1% tetracaine hydrochloride solution into the bladder reduced the average rise to 5/9 mm.Hg, while the individual elevations ranged from 0 to 20 systolic and from 8 to 18 diastolic. Topical anesthesia, therefore, effectively reduced elevation of blood pressure from bladder distention by an average of 77 mm.Hg systolic and 32 mm.Hg diastolic. In four patients the bladder capacity increased during anesthesia.

The blood pressure rise precipitated by either compression of the gonads or distention of the bladder was abolished after subarachnoid alcohol block (2 patients in each category). Increase of blood pressure was noted also following postural changes, such as placing the patient on the abdomen, and during pseudospontaneous spasticity of the skeletal musculature.

*B. Observations During and Following Posterior Rhizotomy.*—No relationship could be established between blood-pressure elevation and particular roots stimulated by the trauma of operation, although in four patients the blood pressure readings indicated higher values during the handling of the thoracic and upper lumbar roots than those of lower segments. The systolic pressure varied during the operation, ranging from 144 to 185 mm.Hg, while the diastolic pressure ranged from 100 to 135 mm.Hg. Electric stimulation of the roots prior to transection had no greater effect on the blood pressure than simple manipulation.

The results of the operation are presented in the Table. In six patients, there was unequivocal improvement, while in the seventh the results were less favorable, although the patient received definite benefit in that he did not suffer from "spontaneous" attacks of hypertension as he had preoperatively.

Headache, severe in all patients preoperatively, was absent in four and rare or mild in three patients.

The blood pressure was severely elevated episodically in all patients even without known distention of hollow viscera. After rhizotomy, such hypertensive episodes were never so severe as before and occurred much less frequently.

The blood pressure rise from gradual physiologic distention of the bladder with urine over a period of one hour improved in all patients postoperatively; the bladder capacity was adequate—i. e., 300 cc. or more—in four patients, remained small (150 to 180 cc.) in two patients, and was not determined in one. Hypertension from acute artificial distention of the bladder was suppressed postoperatively in five patients but still occurred, although less severely, in two. In one of these (T. A.), cystoscopy performed 23 months after rhizotomy caused a transitory high elevation of blood pressure and headache. Both disturbances subsided spontaneously and immediately after removal of the instrument, whereas before the operation both had been protracted even on removal of the exciting cause.

Before the operation, perspiration was severe in all patients. After rhizotomy, it was absent in two, remained profuse in one (H. J.), and was only mild in four. Reflex cutis anserina, present and marked in all patients preoperatively, remained unchanged in three patients; it was considered mild or less frequent by three patients and was completely absent in one.

All patients had reflexogenic erections preoperatively. Only one retrieved full erections 18 months postoperatively, while two others had a return of incomplete erections (50% and 75% respectively). Such erections occurred rarely postoperatively in all three cases.

Pseudospontaneous spasticity was severe in four patients, mild in two, and moderate in one preoperatively. Improvement resulted from rhizotomy in all but one of the cases. The severe spasticity became mild or moderate in three of four patients and was less severe but episodically marked in the fourth. One patient with mild preoperative spasticity became completely flaccid after intervention; the mild spasticity of another remained unchanged. The moderate preoperative spasticity was converted into a mild spasticity and changed from the left side of the body to the right.

Patellar reflexes disappeared in six patients postoperatively. In the seventh patient they returned bilaterally, became exaggerated during the seventh month, then disappeared but were obtainable occasionally on the right side thereafter. Achilles tendon reflexes disappeared in all but the one patient whose knee jerks returned. In this patient they persisted for seven months but were subsequently unobtainable. The Babinski sign disappeared in all patients but in one it was fleetingly present. The bulbocavernosus reflex could be easily elicited in all patients preoperatively; it returned postoperatively in four and was absent in three patients.

Five of the seven patients had suprapubic cystostomy, and two had intraurethral catheterization. After operation, one of the latter started to void incompletely, while the other responded temporarily to pudendal nerve anesthesia. A vesicoureteral reflux present in only one patient disappeared postoperatively despite the abnormal cystoscopic appearance of the ureteral orifices.

COMMENT

Topical or conduction anesthesia was found to be efficient in suppressing or reducing reflex hypertension resulting from noxious stimuli to the skin, urethra, bladder, and testes. Kuhn [4] described the anogenital area as an especially susceptible reflexogenic zone for skeletal spasticity, was found to be equally efficient in producing reflex hypertension in these patients. This observation confirms a statement of Pollock and others [1d] that "as is the case with motor function so [it is] with autonomic nervous system functions."

Aside from the significance which the effect of temporary interruption of afferent pathways had in arriving at the concept of posterior rhizotomy as a procedure for the alleviation of uncontrolled autonomic reflexes, other practical gains were derived from this investigation. Thompson and Witham [1c] pointed to the obvious danger of paroxysmal hypertension during transurethral resection in paraplegics, and heretofore such necessary routine procedures as the change of a catheter, cystoscopy, urethrography, cystography, cystometry, etc., were in some cases followed by hypertension so severe that the repeated administration of high doses of tetraethyl ammonium chloride (etamon®) was necessary. Topical anesthesia of the bladder with 1% tetracaine was found to be efficient in temporarily eliminating this danger during such diagnostic and therapeutic interventions. Nevertheless, topical anesthesia acts apparently only on the mucosal receptors of the bladder, and it cannot prevent hypertension resulting from what appears to be a proprioceptive stimulus of bladder contraction. This selective effect was demonstrated during cystometry of a patient under tetracaine anesthesia whose blood pressure remained low up to the point when, at a volume of 100 cc., uninhibited bladder contractions set in; immediately, a significant rise in blood pressure occurred. These clinical observations are in accordance with the histologic and experimental data of those authors [5] who describe afferent nerves to be distributed in the mucosa and muscularis of the bladder. It appears therefore that visceral function, like somatic, may involve proprioceptive as well as topical surface reflexes, and the two would seem to participate in the uncontrolled autonomic manifestations of patients with lesions of cervical or high thoracic cord segments. Observations on four patients has indicated, moreover, that topical surface anesthesia of anus and rectum with 1% nupercainal® ointment (dibucaine base in hydrous wool fat and petrolatum) will prevent severe attacks of hypertension during the administration of enemas, but the effect of distention of the lower rectal segment after such topical anesthesia is still under investigation.

The indication for such a drastic procedure as posterior rhizotomy will be present in a relatively small number of patients. Since it is known that interventions for the prevention of severe skeletal spasticity are also reserved for a minority of cases, one may conclude that self-limitation of hyperexcitability applies to autonomic and somatic spheres alike. In another respect the indications differ. While procedures to control skeletal spasticity become necessary usually at a rather early stage (within

4. Kuhn, R. A.: Functional Capacity of the Isolated Human Spinal Cord, Brain **73**:1-51, 1950.

5. Langworthy, O. R., and Murphy, E. L.: Nerve Endings in the Urinary Bladder, J. Comp. Neurol. **71**:487-510, 1939. Kleyntjens, F., and Langworthy, O. R.: Sensory Nerve Endings on the Smooth Muscle of the Urinary Bladder, ibid. **67**:367-379, 1937.

the first 24 months) and are rarely indicated after 2 or more years, because of a spontaneous improvement,[1d] autonomic "spasticity" may require intervention even after more than 4 years (two patients, T. A. and H. J.) although it, too, is most marked within the first 24 months.

The upper level of the posterior rhizotomy at the 9th or the 10th thoracic segment was chosen because it has been suggested that all afferent impulses from the bladder reach the spinal cord at or below this area.[6] Guttmann and Whitteridge [1b] have considered that visceral impulses via the hypogastric nerve are of critical importance in initiating these uncontrolled reflexes. We agree with Schumacher and Guthrie,[1f] however, that the posterior sacral roots are an equally important pathway. Thus, since any stimulus, be it cutaneous, proprioceptive, or visceral, can elicit paroxysmal hypertension, a rather extensive posterior rhizotomy appeared preferable to the selective procedure of Foerster,[7] which was designed for the treatment of skeletal spasticity.

The cessation of headache parallels the reduction in blood pressure after operation, as this symptom is known to be associated commonly with hypertensive episodes as well as with distention of intracranial vessels.[1f] Paroxysmal hypertension due to physiologic distention of the bladder was reduced postoperatively in all but one patient (H. J.), and even in this patient the diastolic pressure was lowered after operation. Artificial distention of the bladder did not cause a rise of blood pressure in five of the seven patients. In one of the patients who had a less favorable result (H. J.) the episodes continued after the operation, while in another (T. A.) they were considerably improved, although there was an elevation in blood pressure 22 months and 23 months after rhizotomy, when the bladder was forcibly distended during instrumentation. Here, however, the headache during cystoscopy was fleeting and far less severe than that experienced preoperatively, and it disappeared together with the hypertension immediately after removal of the instrument. No similar episode was noted during forcible distention of the bladder through the suprapubic tube, the simple manipulation of which caused severe hypertensive attacks preoperatively. Any attempt to explain the late postoperative return of autonomic reflexes in this case would be mere conjecture. It is possible that a higher deafferentiation would block impulses which reach the cord from the peritoneal cavity.

In addition to the rather profound alteration on paroxysmal hypertension, several other interesting observations were possible on these patients after posterior rhizotomy. Sudomotor discharges decreased or ceased completely with one exception, but pilomotor reflexes persisted, especially coincident with activity of the rectum prior to and during defecation. Why the reflex arc of cholinergic activity is more susceptible than that of adrenergic is not understood.

So far only 3 patients (L. W., T. A., and H. J.) have regained some of the preoperative erections. Why erections returned in some cases but did not in others

6. Voris, H. C., and Landes, H. E.: Cystometric Studies in Cases of Neurologic Disease, Arch. Neurol. & Psychiat. **44**:118-139, 1940. Learmonth, J. R.: A Contribution to the Neurophysiology of the Urinary Bladder in Man, Brain **54**:147-176, 1931.

7. Foerster, O.: Über eine neue operative Methode der Behandlung spastischer Lähmungen mittels Resektion hinterer Rückenmarkswurzeln, Ztschr. Orthop. Chir. **22**:203-223, 1908; Über die Behandlung spastischer Lähmungen mittels Resektion hinterer Rückenmarkswurzeln, Mitteil a. d. Grenzgeb. Med. u. Chir. **20**:493-558, 1909; Über die Beeinflussung spastischer Lähmungen durch die Resektion hinterer Rückenmarkswurzeln, Deutsch. Ztschr. Nervenh. **41**:146-169, 1911.

is difficult to explain unless one wants to presume that individual variations of anatomical pathways exist in different persons [8] or that the lowermost reflex arc, mediating erection, is not necessarily spinal but peripheral and depends on ganglion cells located in the sex organ. The latter theory is supported by the experience of Marburg and Ranzi,[8] who observed erections in a patient whose cauda equina was completely transsected, as verified at autopsy.

The postoperative return of pseudospontaneous spasticity in some of our patients probably resulted from intersegmental reflex activity of extero- or proprio-ceptive origin from levels above the rhizotomy but below the spinal-cord lesion. Reflex spasms could easily be elicited in such cases by applying noxious stimuli to the skin above the deafferentiated area.

The return of deep reflex activity suggests an incomplete rhizotomy, as it is difficult to explain retained segmental reflexes from a deafferentiated area on any other basis. Foerster [7] noticed absence of ankle jerks regularly after selective posterior rhizotomy including the fifth lumbar and second sacral roots and absence of the knee jerks when the third and fourth lumbar roots were severed. One patient (P. V.) had exaggerated knee and ankle jerks on several occasions during the seventh month after rhizotomy, and this patient, in addition to one other, retained pathological toe signs. Foerster [7] observed persistence of the Babinski sign after his selective rhizotomies, although in his patients the foot tested was not completely deafferentiated.

The bulbocavernosus reflex returned in four of the seven patients, in one as early as two months postoperatively. Although the response is prompt, it is possible that the afferent impulses from the stimulus travel through "auxiliary" sympathetic fibers to segments above the level of rhizotomy, whence they would have to be relayed to the motor outflow of the second to fourth sacral segments. This phenomenon as well as others observed after rhizotomy, requires further clarification. It remains to be seen whether or not an unfavorable prognostic value can be ascribed to the return of this reflex, in view of the fact that two of the four patients displaying a return of this reflex showed, also, postoperative blood pressure rise in response to artificial bladder distention (T. A. and H. J.).

The bladder function remained generally unaltered in these cases, and contracted bladders did not enlarge after the operation (T. A., C. O., and H. J.). One of these patients (H. J.) responded promptly though temporarily to pudendal nerve anesthesia with a balanced bladder function. Inasmuch as his postoperative result was generally considered only fair, this observation must be viewed with caution, and one can state only that the unaltered motor outflow to the muscles of the pelvic floor was accompanied by inhibition to the detrusor despite the interruption of the reflex arc. In two other patients (A. S. and P. V.) signs of detrusor activity appeared for the first time postoperatively, as manifested by reflex micturition or uninhibited contractions of the bladder. These two cases support to some degree the view of Meirowsky and his co-workers [9] that inhibitory impulses to the bladder

8. Marburg, O., and Ranzi, E., cited by Jelliffe, S. E., and White, W. A.: Diseases of the Nervous System: A Textbook of Neurology and Psychiatry, Ed. 6, Philadelphia, Lea & Febiger, 1935.

9. Meirowsky, A. M.; Scheibert, C. D., and Hinchey, T. R.: Studies on the Sacral Reflex Arc in Paraplegia: I. Response of the Bladder to Surgical Elimination of Sacral Nerve Impulses by Rhizotomy, J. Neurosurg. **7**:33-38, 1950.

are mediated through the sacral nerves. A noteworthy observation was the disappearance of a vesicoureteral reflux postoperatively (one case), indicating that this condition may have neurological as well as anatomical causes.[10]

Rhizotomy should include preferably the 9th thoracic segment but at least the 10th thoracic segment. This operation attacks the afferent limb of the reflex arc of the decentralized spinal cord, while a thoracicolumbar sympathectomy, as once considered therapeutically for the condition but not performed,[1b] would interrupt the motor limb. We believe that sympathectomy would be less advantageous than posterior rhizotomy for the following reasons: It is very doubtful that a permanent postural hypotension could be prevented postoperatively in patients who are prone to suffer from that condition spontaneously. Furthermore, two interventions would be necessary, one for each side, thus increasing the operative risk. Finally, respiratory complications would be invited by an operation that of necessity includes the diaphragmatic region and consequently interferes with the only remaining muscle for respiration which in these cases is notoriously diaphragmatic and paradoxical.

So far the operation here reported has been tolerated well by the patients, and there have been no complications. Nevertheless, its indication will be reserved for a relatively small number of patients whose lives are acutely endangered by repeated and unavoidable "spontaneous" episodes of hypertension which threaten to cause subarachnoid cerebral hemorrhage.

## SUMMARY

Patients with lesions of the cervical or upper thoracic spinal cord respond with hypertension to various stimuli from the skin or hollow viscera; the hypertensive response increases as stimulation progresses caudad and becomes maximum at the genitoanal area.

Temporary interruption of sensory pathways from the stimulated area by topical or conduction anesthesia prevents this reflex.

Topical anesthesia of the urethra and bladder is of practical value in preventing these reflexes when instrumentation, such as cystoscopy or transurethral resection, is necessary.

Permanent interruption of the afferent pathways by bilateral posterior rhizotomy below the 9th, 10th, and 11th thoracic segments respectively was done in seven patients.

The operation benefited all patients, although in one the improvement was more limited than in the rest.

The effect of posterior rhizotomy on autonomic and somatic reflex activity is reported and discussed.

Posterior rhizotomy as the method of choice is indicated only when paroxysmal hypertension becomes a threat to the life of the patient.

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10. Talbot, H. S., and Bunts, R. C.: Late Renal Changes in Paraplegia: Hydronephrosis Due to Vesico-Ureteral Reflux, J. Urol. **61**:870-880, 1949. Hutch, J. A.: Vesico-Ureteral Reflux in the Paraplegic: Cause and Correction, Program of the American Urological Association, Chicago, May 21-24, 1951.

# CUTANEOUS NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE)

## Clinical Manifestations and Incidence of Sarcoma in Sixty-One Male Patients

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NEUROFIBROMATOSIS of von Recklinghausen is characterized chiefly by tumor formation of peripheral nerves and pigmentary changes in the skin. Whether the neurofibromas originate from the fibrous connective tissue elements of the nerve sheath or from the sheath of Schwann, and hence whether the disorder involves chiefly mesodermal or ectodermal elements, has been the subject of controversy among pathologists.

The condition is usually recognized by its cutaneous manifestations. These are (1) neurofibroma which may be sessile or pedunculated cutaneous lesions (fibroma molluscum of the older literature) or may be subcutaneous, and (2) areas of pigmentation (café-au-lait spots).

The disease usually runs a benign course and is often noted as an incidental finding. However, the fact that 13 of our patients (21%) are dead or have undergone major surgical procedures as a result of lesions associated with von Recklinghausen's disease testifies to the seriousness of the condition in some patients.

In 10 of our patients (16%) sarcomatous lesions have developed, and at the time of writing, all except one of these are dead or are in the terminal stages of cancer. Interest in the serious complications of this disease and the possibility that earlier recognition of these lesions would improve the prognosis led us to undertake the present study.

### MATERIAL SELECTED

Sixty-one patients with multiple cutaneous neurofibromas examined at the Veterans Administration Hospital, Hines, Ill., between 1931 and 1951 are included in this study. These patients all were veterans, with the exception of the father of one patient and the patient's child whom we were able to examine and follow.

Sixteen other patients carried on the Tumor Registry of Hines Hospital as having neurofibromatosis of von Recklinghausen were excluded from the study because the stigmata of the disease were minimal or the records were too scanty to indicate whether or not the

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disease was definitely present. Five of these had multiple subcutaneous tumors and café-au-lait spots and were excluded from the study because the tumors proved to be lipomas on histologic section. One patient had numerous café-au-lait spots and subcutaneous tumors, one of which was a neurolipoma on microscopic examination. This patient was also excluded from the study. However, this condition probably represents an abortive form (forme fruste) of von Recklinghausen's disease described by many writers.[1] Although pigmentation without neurofibromatosis may be the only manifestation of the disease according to some authors, no patient without cutaneous neurofibromas was included in the present study. Seven such patients were included in the series reported by Sharpe and Young.[2] None of the patients excluded from the study had sarcoma.

## ETIOLOGIC FACTORS

*Incidence.*—The disease is relatively rare. Preiser and Davenport [3] state that it occurs about once in every 2,000 patients that present themselves to medical clinics or private practitioners for skin disease. At Hines Hospital such a diagnosis was made about once in every 4,750 hospital admissions between 1931 and 1951 inclusive. During this period, there were approximately 23,000 patients with malignant neoplasms, 10 of whom had sarcomas associated with von Recklinghausen's disease.

*Sex.*—The sex incidence favors males in about 60% of cases. From reviews of the literature, Thomson [4] states that 63% of patients are males and Preiser and Davenport [3] 51%. Since few female patients are admitted to Hines Hospital, it is not significant that all patients in the present series were males.

*Race.*—The disease has been reported in all races and seems to have about the same incidence in the Negro and the white race. Four of our patients were Negro (7%). Negroes constitute 8% of all patients with neoplastic disease admitted to Hines Hospital.

*Other Factors.*—The etiology of von Recklinghausen's disease, like that of most neoplasms, is unknown. Syphilis has been mentioned as an etiological factor by some.[5] However, among our patients syphilis was present in two (3%), while among patients hospitalized at Hines Hospital approximately 4% are syphilitic. Therefore, there seems to be no etiologic relationship between syphilis and von Recklinghausen's disease.

The heredity of von Recklinghausen's disease has been dealt with at length by numerous authors, particularly by Preiser and Davenport [3] and by Borberg [6] in

1. Eller, J. J.: Incomplete Form of von Recklinghausen's Disease, Arch. Dermat. & Syph. **17**:648, 1928. Feindel, and Oppenheim, R.: Sur les formes incompletes de la neurofibromatose, Arch. gen. med. **2**:77, 1898. Grenet, H.; Ducroquet, R.; Isaac-Georges, P., and Macé, M.: Forme fruste pigmentaire et osseuse de la neurofibromatose, Presse méd. **42**:2060, 1934. Weber, F. P.: Cutaneous Pigmentation as an Incomplete Form of Recklinghausen's Disease, Brit. J. Dermat. **21**:49, 1909. Wise, F., and Eller, J. J.: Recklinghausen's Disease Without Tumor Formation: Incomplete or Abortive Form of the Disease, J. A. M. A. **86**:86, 1926.

2. Sharpe, J. C., and Young, R. H.: Recklinghausen's Neurofibromatosis: Clinical Manifestations in 31 Cases, Arch. Int. Med. **59**:299, 1937.

3. Preiser, S. A., and Davenport, C. B.: Multiple Neurofibromatosis (von Recklinghausen's Disease) and Its Inheritance with Description of a Case, Am. J. M. Sc. **56**:507, 1918.

4. Thomson: On Neuroma and Neurofibromatosis, Edinburgh, Turnbull & Spears, 1900.

5. (*a*) Campana, R.: Syphiloderma: Consecutive Cicatricial Fibromatosis; Multiple Neurofibroma, Bull. R. Acad. Med. Rome **26**:609, 1929. (*b*) Sicoli, A.: Malattia di Recklinghausen e sifilide, Rinasc. med. **7**:142, 1930.

6. Borberg, A.: Clinical and Genetic Investigations into Tuberous Sclerosis and von Recklinghausen's Neurofibromatosis, Acta psychiat. et neurol. Supp. 71, 1951.

the English literature. According to Borberg, inheritance can be demonstrated in about 20% of patients. Six (10%) of our patients reported the disease in members of their immediate family. There are several reasons why this may not represent the true familial incidence of the disease. Routine interviews with patients often are inadequate as to family history, and this is particularly true for von Recklinghausen's disease, since the patient frequently is of subnormal intelligence. Moreover, many people are loath to disclose even to their relatives that they exhibit the stigmata of this disease, and, indeed, such stigmata may be so slight that they entirely escape notice.

## CLINICAL MANIFESTATION

*Neurofibroma.*—Cutaneous neurofibromas were most apparent on the trunk, face, and extremities of these patients. In four patients (7%) neurofibromas were present on the plantar surface of the feet. The largest of these measured 6 by 3 by 3 cm. and was so large that it interfered with walking. The rarity of neurofibroma in this location was the subject of a paper by Herzog,[7] who reported a single case. None of the patients reported in von Recklinghausen's original monograph, published in 1882,[8] had tumors on the plantar surfaces.

Neurofibroma on the palmar surfaces was present in three patients (5%). In addition, two patients had Dupuytren's contractures, one a unilateral lesion and the other bilateral. Ewing [9] believed that there is a relationship between Dupuytren's contracture and von Recklinghausen's disease in some patients.

Intraoral neurofibromas were present in four patients (7%). Two had neurofibromas palpable beneath the buccal mucosa; another had a neurofibroma of the hard palate, and the fourth had a tumor palpable in the tongue. An additional patient stated that a tumor had been removed from the floor of his mouth before we examined him.

No neurofibromas were discovered in the intestinal tract, although upper gastrointestinal roentgenographic studies following a barium meal were made on eight patients and roentgenographic studies of the colon were done on five. No neurofibromas of the intestinal tract were recorded in the protocols of 15 patients on whom autopsies were done. Numerous small neurofibromas were present in the mesentery of the intestine of one patient. Neurofibromatosis of the intestinal tract must be exceedingly rare, although 2 cases accompanied by gastrointestinal hemorrhage have recently been reported by Kleitsch and associates,[10] and 16 cases from the literature were reviewed by Grill and Kuzma [11] in 1942. One of our patients had severe upper gastrointestinal hemorrhage in spite of negative findings in roent-

7. Herzog, E. G.: Neurofibroma of the Sole in a Case of von Recklinghausen's Disease, J. Bone & Joint Surg. **31-B**:227, 1949.

8. von Recklinghausen, F.: Über die multiple Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen, Berlin, A. Hirschwald, 1882.

9. Ewing, J., quoted by Stewart, F. W., and Copeland, M. M.: Neurogenic Sarcoma, Am. J. Cancer **15**:1235, 1931.

10. Kleitsch, W. P.; Kehme, J. H., and Gutch, C. F.: Gastrointestinal Hemorrhage Due to Neurofibromatosis, J. A. M. A. **147**:1434, 1951.

11. Grill, J., and Kuzma, J. F.: Recklinghausen's Disease with Unusual Symptoms from Intestinal Neurofibroma, Arch. Path. **34**:902, 1942.

genograms of esophagus, stomach, and duodenum. In retrospect, a neurofibroma of the small intestine with ulceration seems a possible cause.

Neurofibroma of the central nervous system was proved in three patients—two involving the brain discovered at autopsy and one involving the spinal cord removed

Fig. 1.—Typical neurofibromatosis of von Recklinghausen demonstrating superficial neurofibroma and asymmetrically distributed areas of pigmentation (café-au-lait spots).

at laminectomy. In addition, two patients had clinical evidence of spinal cord tumors, and a diagnosis of neurofibroma of the spinal cord was made.

Elephantiasis neuromatosa is a diffuse overgrowth which results in thickened, loose, heavily pigmented skin which hangs in folds. Such a condition was observed in one patient in this series

*Café-au-lait Spots.*—Areas of cutaneous pigmentation (café-au-lait spots) were present in 38 (62%) of these patients. According to Thannhauser,[12] this increased pigmentation is a localized anatomic anomaly in the cutaneous nerve itself, producing an increase of melanin in the epidermis. Café-au-lait spots are usually distributed asymmetrically on the trunk, less often on the extremities and on the face. Only one patient had café-au-lait pigmentation on the palms and soles. We did not observe areas of abnormal pigmentation on the mucous membranes in any patient.

*Course of the Disease.*—Accurate information regarding the sequence of appearance of cutaneous lesions was available in eight cases. In these patients the areas of pigmentation were present at birth or appeared shortly after and usually preceded the development of cutaneous neurofibroma by several years. In the infant shown

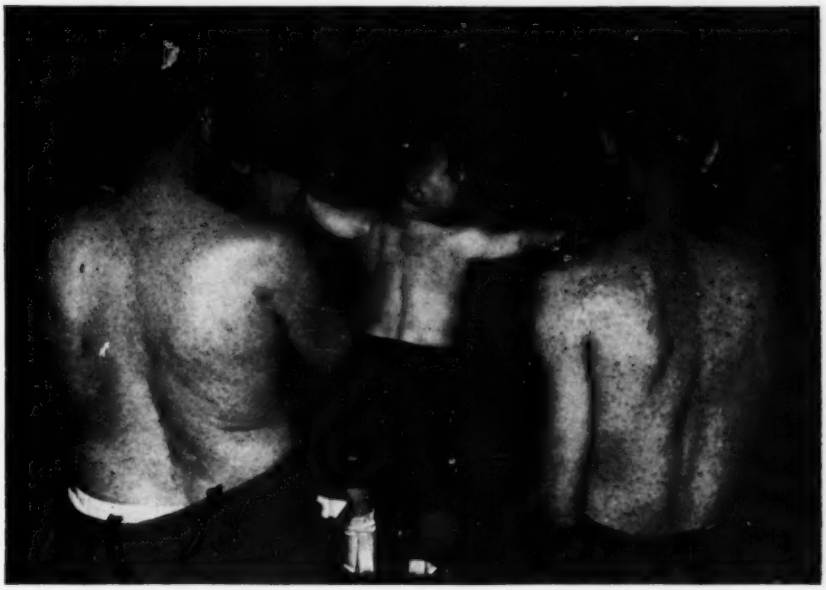

Fig. 2.—Neurofibromatosis of von Recklinghausen in three generations. Café-au-lait spots were first noticed on infant's skin when he was 2 months old. A neurofibroma appeared on the infant's forehead when he was 8 months old, and subsequently neurofibromas appeared on his scalp, ears, and chest.

in Figure 2 café-au-lait spots developed when he was 2 months of age. Subsequently, a neurofibroma appeared when he was 5 months old and others at frequent intervals thereafter.

Usually the disease progresses during the life span of the person, but it may remain stationary for long periods. Certain factors seem to provide a growth stimulus, particularly puberty and pregnancy.[13] Some cases are reported in which

12. Thannhauser, S. J.: Neurofibromatosis (von Recklinghausen) and Osteitis Fibrosa Cystica Localisata et Disseminata (von Recklinghausen), Medicine **23**:105, 1944.

13. (*a*) Knapp, A. A.: von Recklinghausen's Disease, M. Rec. **139**:62, 1934. (*b*) Sharpe, J. C., and Young, R. H.: Neurofibromatosis: The Effect of Pregnancy on Skin Manifestations, J. A. M. A. **106**:682, 1936. Sharpe.[2]

trauma, infection, and the menopause seem to produce increase in growth of the cutaneous lesions.[14]

The cutaneous neurofibromas usually appear during the early years of life, and many patients state that the lesions were present at birth or appeared soon thereafter. Among our patients, there was an additional high incidence of lesions developing in the decade from 21 to 30 years (Table 1).

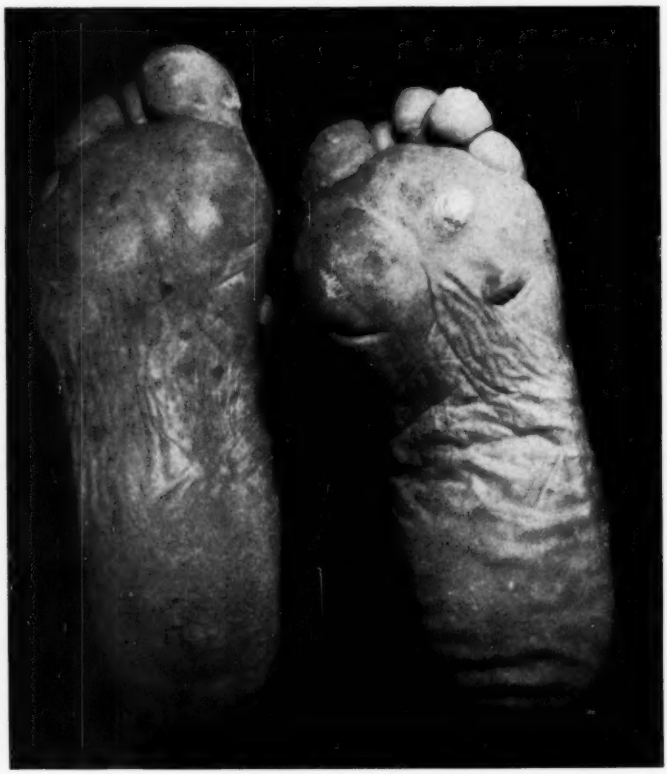

Fig. 3.—Neurofibroma on soles.

TABLE 1.—*Age at Appearance of Neurofibroma*

| Age, Yr. | All Patients | Patients with Sarcoma |
|---|---|---|
| 0-10 | 19 | 4 |
| 11-20 | 7 | 1 |
| 21-30 | 17 | 2 |
| Over 31 | 5 | 1 |
| Unknown | 13 | 2 |
| Total | 61 | 10 |

14. Sharpe,[2] Knapp.[13a]

*Osseous Lesions.*—The commonest bone lesion associated with von Recklinghausen's disease is scoliosis, which may be a primary condition or may be compensatory to inequality of length of the long bones of the lower extremity. Scoliosis or kyphoscoliosis was present in 11 patients (18%) of this series. Other bony defects which have been described by Brooks and Lehman [15] and by Thannhauser [12] are (1) subperiosteal cysts, (2) localized osteoporosis (present in one of our patients), (3) giantism of one bone, (4) pseudoarthrosis, and (5) subperiosteal tumors.

*Congenital Lesions.*—Congenital lesions occur with frequency in patients with von Recklinghausen's disease. In this series one would not expect to find many patients with congenital lesions because all but two of them had previously been accepted for military service. In spite of this, one patient had bilateral undescended testicle, and one had hypospadias. In addition, eight had inguinal hernias and one had a foramen of Morgagni hernia.

*Ocular Lesions.*—Ocular disease is less frequently associated with von Recklinghausen's disease and was present in 11 of our patients. Detachment of the retina, which was the commonest finding, was caused by sarcoma of the eyeball in one patient, and in three the cause was not stated.

Tumor of the optic nerve was proved in one patient at autopsy and suspected in three other patients who had optic atrophy. Davis [16] points out that the term "neurofibroma" should be abandoned for these lesions because they are usually gliomas or endotheliomas.

A variety of other ocular conditions was encountered, including corneal opacities (four patients), neurofibroma of the eyelids (two patients), and unilateral exophthalmos due to intracranial tumor (one patient).

*Other Lesions.*—One patient had acromegaly associated with pituitary tumor, and one patient had bilateral gynecomastia. In the remaining 59 patients, signs other than cutaneous pigmentation to suggest endocrine dysfunction were lacking.

Mental disorders are common in von Recklinghausen's disease and existed to a disabling degree in 12 patients. Three of the four patients who had grand mal seizures also had clinical evidence of intracranial tumor. Other mental disorders of significance are listed in Table 2.

### SARCOMA ASSOCIATED WITH VON RECKLINGHAUSEN'S DISEASE

The most serious complication of von Recklinghausen's disease is sarcoma, which occurred in 10 patients in this series, an incidence of 16%. This figure may not represent the true incidence of sarcoma in this disease because the exact incidence of von Recklinghausen's disease itself is unknown. The incidence given by Hosoi,[17] who reviewed 65 cases of sarcoma in von Recklinghausen's disease reported

15. Brooks, B., and Lehman, E. P.: Bone Changes in Recklinghausen's Neurofibromatosis, Surg., Gynec. & Obst. **38**:587, 1924.

16. Davis, F. A.: Primary Tumors of the Optic Nerve (A Phenomenon of Recklinghausen's Disease): A Clinical and Pathologic Study with a Report of 5 Cases and a Review of the Literature, Arch. Ophth. **23**:735 and 957, 1940.

17. Hosoi, K.: Multiple Neurofibromatosis (von Recklinghausen's Disease), Arch. Surg. **22**:258, 1931.

in the literature prior to 1931, was 13%. Many abortive forms of the disease were included in Hosoi's calculation, and our incidence would have been lower if we had also included abortive forms. Both figures are probably too high—ours because

TABLE 2.—*Clinical Manifestations in Sixty-one Patients with Neurofibromatosis of von Recklinghausen*

| | Patients | |
|---|---|---|
| | No. | % |
| Tumors with pigmentation | 38 | 62 |
| Tumors without pigmentation | 23 | 38 |
| Plexiform neurofibroma | 2 | 3 |
| Elephantiasis neuromatosa | 1 | .. |
| Osseous changes | 12 | 20 |
| Vertebrae | 11 | |
| Skull | 1 | |
| Mental disorders * | 12 | 20 |
| Epilepsy | 4 | |
| Mental inferiority | 4 | |
| Psychosis | 2 | |
| Neurosis | 4 | |
| Congenital defects | 11 | 18 |
| Inguinal hernia | 8 | |
| Foramen Morgagni hernia | 1 | |
| Undescended testicle | 1 | |
| Penile hypospadias | 1 | |
| Ocular disease * | 11 | 18 |
| Optic atrophy | 3 | |
| Detached retina | 4 | |
| Neurofibroma of optic nerve | 1 | |
| Neurofibroma of eyelid | 2 | |
| Myelinated nerve fibers in retina | 2 | |
| Amyloid disease | 1 | .. |
| Acromegaly | 1 | .. |

* In some patients more than one condition existed.

TABLE 3.—*Sarcoma in Patients with von Recklinghausen's Disease*

| | |
|---|---|
| Total no. of patients | 10 |
| Total no. of sarcomas | 11 |
| Location | |
| Thigh | 4 |
| Retroperitoneal | 2 |
| Neck | 2 |
| Shoulder | 1 |
| Sacrum | 1 |
| Eyeball | 1 |
| Inoperable sarcomas | 2 |
| Patients submitted to surgery | 8 |
| Nonresectable sarcomas | 2 |
| Resections for primary sarcoma | 7 |
| Resections for recurrent sarcoma | 2 |
| Patients living 5 years after resection | 3 |
| Patients with metastases | 5 |

many patients with von Recklinghausen's disease are relatively healthy and therefore tend to stay away from the hospital and Hosoi's because of the tendency of authors to report complicated cases and those with a malignant course rather than

those in which the disease follows a benign course. Borberg [6] found only one patient with sarcoma in 76 living patients with the disease whom he examined. The data on our patients are given in Tables 3 and 4. Most notable features of these lesions are their tendency to grow slowly, to recur after surgical excision, and to metastasize via the blood stream late in the course of the disease.

Patients with sarcoma were not strikingly different from those without sarcoma in regard to the other manifestations of the disease. Areas of cutaneous pigmenta-

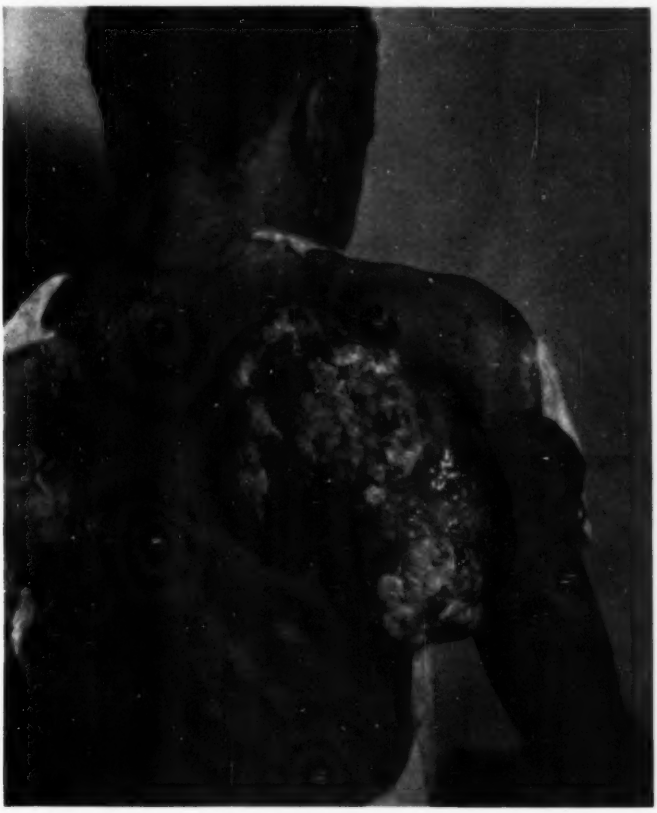

Fig. 4 (Case 7, Table 3).—Sarcoma in patient with neurofibromatosis of von Recklinghausen.

tion occurred in 80% of patients with sarcoma and in 59% of patients without sarcoma. However, the age of appearance of neurofibroma, family history of the disease, and number and distribution of neurofibromas and of areas of pigmentation were approximately the same in the two groups.

*Origin.*—The site of origin of four sarcomas was the thigh; two originated in the neck, two in retroperitoneal structures, and one each in the shoulder, sacral area, and eyeball. Eight of the sarcomas developed in deep tissues either within

TABLE 4.—*Sarcoma in von Recklinghausen's Disease*

| Case No. | Race | Age at Onset of Symptoms, Yr. | Location | Onset and Course | Type of Treatment | Pathology | | Follow Up |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Gross | Microscopic | |
| 1 | W | 56 | Left eyeball | Feb., 1947, loss of vision in left eye developed over three-month period; June, 1947, retinal detachment | June, 1948, enucleation left eye, postoperative x-ray therapy | 1.5 by 1 by 1 cm. hard tumor | Spindle-cell sarcoma | Living, no evidence of sarcoma 14 yr. after first symptoms, 12 yr. after enucleation |
| 2 | W | 34 | Within deep muscles of posterior thigh | 1926, appearance of slowly growing tumor | 1934, surgical excision | Hard, white 7.5 by 7.5 by 5 cm. tumor partially encapsulated with extension distally and proximally | Fibrosarcoma | Suicide 15 yr. after onset, 7 yr. after resection; no necropsy |
| 3 | N | 29 | Lateral aspect right thigh deep to vastus lateralis and rectus femoris | 1946, appearance small tumor, gradual increase in size | Nov., 1950, wide resection; May and Oct., 1951, wide resection of recurrences; Jan., 1952, lumbar laminectomy and biopsy of metastatic sarcoma spinal cord | (1) Original tumor, hard, grayish-yellow noninfiltrating, encapsulated, lobulated 12 by 5 by 5 cm.; (2) first recurrence, hard, encapsulated 10 by 8 by 8 cm.; (3) second recurrence partially infiltrative, partially encapsulated, hard 15 by 10 by 6 cm. tumor | Primary and recurrences, low grade neurogenic sarcoma | Living with recurrence and metastasis to spinal cord, Jan., 1952, 16 yr. after onset, 4 mo. after last resection |
| 4 | W | 28 | Deep to muscles of right posterior neck | Oct., 1948, appearance of tumor | Dec., 1948, excision of tumor and x-ray therapy to posterior neck region (elsewhere); June, 1949, recurrence | (1) Gross pathology of primary unknown; (2) recurrence, 10 by 10 by 10 cm.; hard tumor with erosion of occipital bone and transverse processes of cervical spine | Spindle-cell sarcoma (primary and recurrence) | Died 1 yr. after onset, 9 mo. after excision of tumor; pulmonary and cerebral metastases at necropsy |
| 5 | W | 40 | Sacrum | 1938, pain in sacrum and in rectum 15 months before hospital admission | Tumor inoperable; x-ray therapy without effect | Extensive tumor involving pelvis with erosion of sacrum | Spindle-cell sarcoma | Died 2½ yr. after onset; metastases to lung at necropsy |
| 6 | N | 50 | Apparently in deep tissues lateral aspect left thigh | 1948, onset of swelling right thigh; rapid progress | None | Firm, indurated; grossly infiltrative | Tissue not obtained | Died 1 yr. after onset; extensive sarcoma, thigh; no necropsy |
| 7 | N | 27 | Overlying spine of right scapula, superficial to superficial fascia | 1919, gradual appearance of tumor at site of removal of benign tumor one year previously; 1936, increase in size of tumor; April, 1937, tumor became ulcerated | Nov., 1937, excision of tumor and skin graft | Primary, large fungating tumor (Fig. 4); recurrence similar to primary | Fibrosarcoma | Died 21 yr. after onset; 15 mo. after surgical excision; metastases to lungs and adrenal at necropsy |

| Case No. | Race | Age at Onset of Symptoms, Yr. | Location | Onset and Course | Type of Treatment | Pathology | | Follow-Up |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Gross | Microscopic | |
| 8 | W | 51 | Retroperitoneal right abdomen | June, 1945, appearance of right lower quadrant mass | Sept., 1945, exploration and biopsy of nonresectable tumor; x-ray therapy to right abdomen without effect | Firm, fibrous encapsulated mass extending from pelvis to right costal margin | Fibrosarcoma | Died 6 mo. after onset, 3 mo. after exploration; presumably from abdominal sarcoma; no necropsy |
| 9 | W | 23 | Beneath rectus femoris muscle left thigh adjacent to periosteum of femur | Jan., 1947, onset pain and appearance of tumor, gradual increase in size | April, 1948, resection; recurrence two months later | Hard encapsulated 5 by 5 by 10 cm. tumor | Neurogenic sarcoma | Died 2 yr. after onset, 8 mo. after resection of sarcoma of femur; generalized metastasis at necropsy |
| 10 | W | 24 | (1) Posterior cervical region | (1) Gradual swelling of neck | (1) 1946, excision of sarcoma of neck (elsewhere) 2 mo. after onset | (1) Unknown | (1) Fibrosarcoma (report from Cook County Hospital) | (1) No recurrence sarcoma of neck 5 yr. after excision |
| | | 29 | (2) Retroperitoneal, left lower quadrant abdomen and pelvis | (2) Gradual appearance of tumor on abdomen | (2) 1951, exploration and biopsy of nonresectable tumor, left lower quadrant abdomen 4 mo. after onset; postoperative x-ray therapy | (2) Large partially encapsulated tumor fixed to femoral vessels | (2) Neurofibrosarcoma | (2) Living with large tumor, pelvis 5 mo. after onset, 3 mo. after exploration |

the deep muscles of the thigh (four sarcomas), or neck (one sarcoma), or in the retroperitoneal tissues (two sarcomas), or sacrum (one sarcoma). One sarcoma developed in superficial tissue (Fig. 4). We were unable to determine whether or not it developed in a cutaneous neurofibroma because when it was first observed it was so large that its site of origin had been obscured. We do know that it remained superficial to the superficial fascia overlying the scapula. One sarcoma (Case 10, Table 4) occurring in the muscles of the neck was removed before we examined the patient, and we were unable to determine whether it arose from deep or superficial structures. Although our number of cases is small, it seems evident that sarcomas associated with neurofibromatosis of von Recklinghausen usually arise in deep structures but occasionally arise superficially.

Six patients who had sarcomas had extensive cutaneous neurofibromatosis, but four others had only a few cutaneous neurofibromas. One patient who had two primary sarcomas had very few cutaneous neurofibromas (Case 10, Table 4). In many patients with extremely numerous cutaneous neurofibromas no sarcomas were present. Therefore no definite relationship seemed to exist between sarcoma and the number of cutaneous lesions.

*Pathology.*—Tissue for microscopic study was obtained from 10 of 11 sarcomas. In Case 6 (Table 4) the tumor was diagnosed as sarcoma in spite of the lack of microscopic confirmation. The tumor of the thigh in this patient was so large and developed so rapidly that sarcoma seemed the most probable diagnosis.

The histologic structure of these lesions was described as fibrosarcoma, spindle-cell sarcoma, and neurogenic sarcoma by the various pathologists who examined them. No attempt to grade these tumors was made. The proper terminology for these tumors has been a subject of discussion by Stout,[18] who considers fibrosarcoma and malignant schwannoma the most adequate terms, and Stewart and Copeland,[19] who prefer the term neurogenic sarcoma. Since this is primarily a clinical study, the histology of these tumors will not be dealt with further.

Grossly these tumors tend to be circumscribed and encapsulated. In Case 2 (Table 4) the tumor extended distally and proximally along the course of the sciatic nerve. In Case 10 the retroperitoneal tumor was partially encapsulated but along its posterior surface was intimately adherent to the iliac vessels. With each recurrence these tumors tend to become increasingly less encapsulated and more infiltrative, as illustrated by Case 3 (Table 4).

*Treatment and Prognosis.*—Treatment of patients with sarcoma in most cases was unsatisfactory. Three patients with sarcoma apparently were cured by surgical removal of the tumor (Cases 1, 2, and 10, Table 4), as evidenced by survival times of 12, 7, and 5 years without demonstrable recurrences. One of these patients (Case 10, Table 4) is now dying of a primary retroperitoneal sarcoma five years after surgical removal of a sarcoma from the neck.

Two patients had inoperable sarcomas (Cases 5 and 6, Table 4), and an additional two underwent exploratory operations but had nonresectable sarcomas (Cases 8 and 10, Table 4).

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18. Stout, A. P.: The Malignant Tumors of the Peripheral Nerves, Am. J. Cancer **15**:1235, 1937. Stout, A. P.: Atlas of Tumor Pathology: Tumor of the Peripheral Nervous System, Washington, D. C., Armed Forces Institute of Pathology, 1949.

19. Stewart, F. W., and Copeland, M. M.: Neurogenic Sarcoma, Am. J. Cancer **15**:1235, 1931.

Metastatic sarcoma was proved in five patients. In four who succumbed to sarcoma, metastatic lesions were present in the lungs at necropsy (Cases 4, 5, 7, and 9, Table 4). One patient, who is still living (Case 3, Table 4), has recently had a lumbar laminectomy and biopsy of a sarcomatous lesion, probably metastatic from a recurrent sarcoma of the thigh.

In three patients recurrences developed after resections for sarcoma (Cases 3, 4 and 7, Table 4). In each, local resections of the tumors had been done, with considerable sacrifice of surrounding normal tissue. A recent patient (Case 3, Table 4) was advised to have a disarticulation of the hip for sarcoma in the thigh. This was refused, and the tumor already has recurred twice after wide local resections. Distant metastases in this patient were not apparent until six years after appearance of the primary tumor and three months after the patient's second resection for recurrence. A more radical procedure (disarticulation of the hip joint or hemipelvectomy) done earlier in the course of the disease might have saved this patient.

Roentgen therapy to skin tolerance was given to four patients (Cases 4, 5, 8, and 10), but no regression of any tumors was observed.

Nine patients with sarcoma had received no treatment for the condition previous to reporting to Hines Hospital. One of these lesions (Case 1, Table 4) situated in the eyeball was small and measured 1.5 by 1 by 1 cm. In the other eight patients the tumors were large (Cases 2, 3, 5, 6, 7, 8, 9, and 10, Table 4), varying from approximately 7.5 to 22 cm. in their greatest diameters. Duration of symptoms before admission for treatment in these eight patients varied from 3 months to 12 years (average 2 5/12 years). It is evident that most of these patients reported for treatment only after their sarcomas had become large and had been present for many months. In the interest of improving the prognosis, patients with von Recklinghausen's disease should be taught to report for frequent routine examinations and seek treatment immediately if a deep-seated growth is suspected. Physicians examining these patients should look particularly for tumors palpable in the deep tissues, as these tumors are most likely to be sarcomatous.

*Other Neoplastic Disease.*—In addition to the 10 patients with sarcoma, 4 others had malignant neoplasms, making the total incidence of malignant disease among 61 patients 23%. Two of these lesions were epidermoid carcinomas of the skin, one a basal cell epithelioma, and one a squamous cell epithelioma. Both these lesions occurred on the faces of senile persons independent of neurofibroma. The significant neoplasms in this group of patients are listed in Table 5.

## COMMENT

*Risk of Biopsy or Excision of Benign Neurofibroma.*—It has been stated by some that biopsy or extirpation of benign neurofibromas involves hazard and may be followed by the appearance of neurofibroma elsewhere in the body or may contribute to sarcomatous degeneration either of the lesion from which the biopsy specimen was taken or of a lesion distantly located.[20] We have been aware that

20. (*a*) Charache, H.: Neurogenic Sarcoma, Am. J. Surg. **41**:275, 1938. (*b*) Herrmann, J.: Sarcomatous Transformation in Multiple Neurofibromatosis (von Recklinghausen's Disease): Report of 4 Cases, Ann. Surg. **131**:206, 1950. (*c*) Pitts, H. H.: Neurofibromatosis of Urinary Bladder, Urol. & Cutan. Rev. **53**:623, 1949. Sharpe.[18b]

this attitude exists but, nevertheless, have excised lesions when we considered it indicated for therapeutic, diagnostic, or cosmetic reasons. In general, we prefer total excision or excision biopsy of a lesion when feasible rather than a biopsy involving partial excision.

We have examined the histology of 74 benign neurofibromas excised from 32 of these patients. In addition, 67 other supposedly benign lesions which we did not examine were removed at other hospitals. This makes a total of 141 benign lesions removed from 34 of these patients during or prior to the time that they were under our observation.

In no case did we observe acceleration of growth of any lesions which we could definitely attribute to excision of these tumors. Only once (Case 7, Table 4) did we observe the later appearance of a sarcomatous lesion at the site of removal of a benign lesion. Occasionally we observed new benign cutaneous lesions developing subsequent to excision of a benign lesion, but in each case this seemed to be in

TABLE 5.—*Neoplastic Disease in 61 Patients with Neurofibromatosis of von Recklinghausen**

| | No. of Patients | No. of Lesions |
|---|---|---|
| Associated with von Recklinghausen's Disease | | |
| Cutaneous neurofibroma | 61 | .. |
| Sarcoma | 10 | 11 |
| Brain tumor (2 benign, 1 malignant, 6 type undetermined) | 9 | .. |
| Spinal cord tumor (1 proved neurofibroma, 2 probably neurofibroma) | 3 | 3 |
| Mediastinal tumor (probably neurofibroma) | 2 | 2 |
| Mediastinal cyst (probably meningocele) | 1 | 1 |
| Neurofibroma of the mesentery | 1 | 1 |
| Apparently not Associated with von Recklinghausen's Disease | | |
| Chromophile adenoma of pituitary with acromegaly | 1 | 1 |
| Mixed tumor of parotid | 1 | 1 |
| Adenoma ampulla of Vater | 1 | 1 |
| Gynecomastia | 1 | 1 |
| Dupuytrens contracture | 2 | 3 |
| Epidermoid carcinoma (skin) | 2 | 2 |
| Leucemia | 1 | 1 |

* Many of these patients had cutaneous lipoma, angiomas, and sebaceous cysts. These lesions are not tabulated.

keeping with the natural progress of the disease and not to be related to the trauma or stimulus provided by excision of the lesion.

All the cutaneous lesions which clinically appeared to be benign were also benign under the microscope, and none showed evidence of early sarcomatous change. This observation and the fact that all except one of the sarcomas in this series arose in deep structures led us to believe that cutaneous neurofibromas rarely if ever undergo sarcomatous change.

*Risk of Surgery.*—Various authors have reported shock, hemorrhage, and death occurring during major surgery in patients with von Recklinghausen's disease.[21] Phillips [21b] has stated that these patients present an increased surgical risk. Twenty-three major operations were performed on our group of patients at Hines Hospital, and an additional 11 operations were performed elsewhere, making a total of 34

21. (*a*) Jackson, A. H.: Three Cases of Multiple Neurofibromatosis with Malignant Degeneration, J. Nerv. & Ment. Dis. **78**:581, 1933. (*b*) Phillips, H. T.; Ferri, L. B., and Morginson, W. J.: Surgical Risk Accompanying von Recklinghausen's Disease, West Virginia M. J. **28**:263, 1932. Sharpe, J. C., and Young, R. H.: Footnotes 2 and 13*b*.

major operative procedures done on 27 patients. There was no operative mortality, no unusual hemorrhage encountered while the patients were on the operating table or during the postoperative periods, and no difficulties which would lead us to believe that the risk of surgery is increased in patients with von Recklinghausen's disease. It seems to us that von Recklinghausen's disease in itself does not contraindicate surgery.

*Causes of Death in Patients with von Recklinghausen's Disease.*—It has often been stated that patients do not die because of the disease but die with it. However, of 22 patients in this series who are dead, 8 died as the result of von Recklinghausen's disease. Six of these died of sarcoma and two of neurofibroma of the brain. One patient with intracranial neurofibroma had multiple tumors, including a cerebellopontine angle tumor; the second had a neurofibroma at the roof of the third ventricle, producing a fatal hydrocephalus.

Two additional patients died of brain tumors. One had a malignant tumor of the left cerebral hemisphere, which on histologic study proved to be a glioblastoma multiforme. No autopsy was permitted on the second patient and the exact nature of the tumor therefore remains undetermined.

TABLE 6.—*Causes of Death of Patients with von Recklinghausen's Disease*

| | | |
|---|---|---|
| Neoplastic disease | | 12 |
| Sarcoma | 6 | |
| Brain tumor | 4 | |
| Carcinoma | 1 | |
| Leukemia | 1 | |
| Cardiovascular disease | | 6 |
| Pneumonia | | 1 |
| Suicide | | 1 |
| Tuberculosis | | 1 |
| Cirrhosis of the liver | | 1 |
| Total | | 22 |

Other causes of death are listed in Table 6. Six patients died of cardiovascular disease and eight of a variety of causes.

## SUMMARY

The principal clinical manifestations and associated lesions in 61 patients with cutaneous neurofibromatosis (von Recklinghausen's disease) are tabulated.

The most serious complication of the disease is sarcoma, which occurred in 10 cases (16%). Osseous changes, mental disorders, congenital defects, and ocular disease occur in about 20% of patients.

Sarcomas in patients with von Recklinghausen's disease usually arise in deep structures, and rarely if ever do cutaneous neurofibromas undergo sarcomatous degeneration.

Like other soft-tissue sarcomas, they require radical surgical excision. They tend to recur locally after surgery, metastasize via the blood stream late in the course of the disease, and have a poor prognosis.

Neurofibromatosis of von Recklinghausen in itself is not a contraindication to surgery, nor does it increase the surgical risk.

# METABOLIC MANAGEMENT OF ADVANCED PROSTATIC CANCER

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THIS YEAR marks the 10th anniversary of the inception of the treatment of prostatic cancer by means of the administration of certain estrogenic-like substances, on the one hand, and castration, on the other. Contributions in this field have been many and most valuable, not only in the field of prostatic cancer alone but in the much broader field of the chemical aspects of cancer in general. From all these many contributions and observations has evolved what appears to be a fairly reasonable and rational plan of management. This plan is as follows: First of all, there is no controversy as to whether prostatic cancer should be removed surgically. Our main problem in surgical indications at the present time involves chiefly the extent to which one chooses to perform surgery. It will be quite some time, unfortunately, before an appraisal of end-results will make it possible to determine how radical surgery should be. Colston [1] has given diethylstilbestrol in inoperable cases and converted them into reasonable surgical-approach cases. Neither castration nor the administration of any of the estrogenic substances should be instituted if there is no discomfort and if the status of the patient is such that he can carry on his necessary activities without handicap. If interference with emptying the bladder is the sole complaint, undoubtedly transurethral resection is the procedure of choice. Repeated resections, if necessary, should be done. When pain becomes a symptom and when the general trend of the patient's condition is unsatisfactory and downward, then castration should be the procedure of choice. There are certain circumstances in individual case problems that sometimes make it advisable to institute the administration of some of the estrogenic-like substances rather than castration. These circumstances involve the attitude of the patient toward castration, which we may not be able to satisfactorily control or adjust. Another circumstance in which the administration of the estrogenic-like substances seems advisable is that in which the patient can best be kept in a state of ignorance of the diagnosis by this type of treatment. Radiation castration as described by Munger,[2] while not as certain as surgical castration, adds an additional form of therapy which may readily be employed when circumstances concerning the attitude of the patient preclude surgery but will allow of radiation castration. Munger calls attention to the possibility of the radiation having an influence in the adjoining areas which may be beneficial.

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Read before the Section on Urology at the One-Hundredth Annual Session of the American Medical Association, Atlantic City, June 13, 1951.

1. Colston, J. A. C., and Brendler, H.: Endocrine Therapy in Carcinoma of Prostate: Preparation of Patients for Radical Perineal Prostatectomy, J. A. M. A. **134**:848-853, 1947.

2. Munger, A. D.: Experience in Treatment of Carcinoma of the Prostate with Irradiation of the Testicles, J. Urol. **46**:1007-1011, 1941.

When the effectiveness of castration has run its course, the administration of the various estrogenic-like substances should be instituted. Herein lies the problem of appropriate dosage. The smallest possible dose which will accomplish the desired response is the proper dose, and this may vary from 1 mg. to 100 mg. or more a day administered orally, by hypodermic injection, or by the implantation of pellets. Conversely, when the ability to control the clinical trend by the administration of the estrogens has become unsatisfactory, castration in some instances will produce an additional period of satisfactory trend and should be done. For some patients the administration of testosterone, as reported by Scott [3] and his co-workers, will result in short-lived improvement.

Adrenalectomy was not indicated in the light of the reports previously made by Huggins,[4] Scott, and their co-workers. However, at the 1951 Annual Meeting of the American Urological Association, Thorn, Harrison, and Criscitiello described adrenalectomy done on 13 patients who were very bad risks for hypertension, with 4 deaths. This, of course, suggests the possibility of performing bilateral adrenalectomy on patients with carcinoma of the prostate and supporting them with substitution therapy of cortisone, desoxycorticosterone acetate, whole adrenal extract, and electrolytic balancing. I understand that the Huggins and Thorn group are carrying on observations in this field. The financial burden of chemical maintenance in these cases will add appreciably to the present increasingly difficult problem of rising medical-care costs.

Pituitary irradiation sometimes proves of value, and there is no reason for not instituting such treatment on a trial and failure basis. The control of pain is many times a very difficult problem, and simple agents, such as acetylsalicylic acid-acetophenetidin-caffeine tablets (empirin® compound) and codeine, gradually going into the stronger acting narcotics, are indicated. The administration of the B-complex vitamin group will sometimes prove to be of value indirectly in the control of pain. Local roentgen radiation to painful areas is very effective at times. As a last resort, prefrontal lobotomy in proper hands will be found to be appropriate in certain situations. Throughout the entire period of observation and treatment, the problem of general support is most important. The hemogram indicates whether ordinary hematinics are adequate or whether blood transfusions are necessary. Adequate support sometimes calls for numerous and frequent blood transfusions. Polyvitamins are frequently very effective in general support, and their administration should be instituted as soon as the trend is unsatisfactory. The tongue is indicative of marked deficiencies. General encouragement and an optimistic attitude on the part of the physician, while not frequently mentioned, is just as important here as in most urological problems encountered, or probably more important.

### ACID PHOSPHATASE

The value of acid-phosphatase estimation has resolved itself into a confirmation test of identifying extensive osseous abnormality as being due to prostatic carcinomatous metastases. It is of no value as an early diagnostic measure when the

3. Brendler, H.; Chase, W. E., and Scott, W. W.: Prostatic Cancer: Further Investigation of Hormonal Relationships, Arch. Surg. **61**:433-440, 1950.

4. Huggins, C., and Scott, W. W.: Bilateral Adrenalectomy in Prostatic Cancer, Ann. Surg. **122**:1031-1041, 1945.

lesion is confined to the original site, unless the experience of Herbert [5] proves to be of value. In rare instances it is paradoxical, most likely due to exhaustion when the estimation is below 4 units in the face of extensive osseous metastases and terminal morbidity.

The closest anyone has come to carrying out a promising qualitative test is the method described by Herbert, in which she demonstrated that prostatic acid phosphatase in normal serum is destroyed by alcohol but that acid phosphatase in normal serum (produced by extraprostatic tissue) is alcohol-stable. She found that the moderate increase in serum acid phosphatase sometimes found in Paget's disease is all "alcohol-stable," whereas in metastasizing prostatic carcinoma, with raised serum acid phosphatase, treatment of the serum with alcohol lowers the titer to normal. Even when the total serum acid phosphatase titer is not raised, a significant amount of prostatic phosphatase in the serum may suggest prostatic carcinoma.

### SEDIMENTATION RATE

The value of the sedimentation rate, as described by Kearns,[6] has been the most reliable single test as an indicator of the general clinical trend of the patients that I have observed.

### CHYMOTRYPSIN AND RENNIN

At the last meeting of the American Urological Association, West, Malcolm, and Rusche found that there was a close correlation between the concentration of the enzymes chymotrypsin and rennin and the clinical course of the cancer. They used their estimates as a guide to the dosage to be employed when the steroids were administered therapeutically. This contribution might possibly prove of some value in future therapy.

### THE STEROIDS

There are 46 steroids identified in the urine. Quantitative patterns of these steroids are most interesting and complex. Much has been done in urinary steroid pattern analysis, but no complete patterns have been done to date, and this is chiefly because of the unavailability of adequate laboratory facilities. To date, Dobriner and his associates and May have made the most contributions in this field. Dobriner [7] has shown that etiocholanolone in increased amounts may mean cancer in both male and female. May [8] demonstrated (1) that there was no consistent difference in the total amount of estrogen excreted by patients with carcinoma of the prostate and by those with no demonstrable prostatic disease; (2) that the presence or absence of the testes appeared to produce no alteration of the total estrogen excretion and no alteration in the pattern of distribution of estrone, estradiol, and estriol in the urine of either group of patients, and (3) that the patients with carcinoma showed a tendency (75%) to convert exogenous estrone to estriol more readily than did the patients without cancer, although one of the five patients with

5. Oelbaum, M. H.: Medical Aspects of Carcinoma of the Prostate with Secondary Deposits in the Bone, Lancet **1**:811-813, 1950.

6. Kearns, W. M.: Treatment of Carcinoma of the Prostate with Estrogens, Wisconsin M. J. **41**:575-581, 1942.

7. Lieberman, S., and Dobriner, K.: Steroid Hormones, Madison, Wis., University of Wisconsin Press, 1950.

8. May, J. A.: Estrogen Excretion Studies in Patients with Carcinoma of the Prostate Gland, Urology, Correspondence Club Letters, Dec. 15, 1947.

nonprostatic cancer studied behaved similarly. There are many interesting problems concerning the steroids that we should like to have the answer to in the future. Some which suggest themselves are as follows: 1. How does the complete steroid pattern of patients castrated compared with that of the patients who are given estrogen? 2. How do the patients who respond to either therapy differ, or do they differ, from the patient who does not respond? 3. How do different dosages of estrogen affect these patterns?

A current contribution by Grayhack and Harris at the 1951 Meeting of the American Urological Association reported these authors' observations on the influence of shifting the adrenal blood channels from the general to the portal circulation. They observed that the liver inactivated the androgen but that the life-sustaining adrenal steroids were not completely inactivated. These observations are a most valuable contribution in this steroid problem.

In view of the fact that renal metabolism must vary and that the likelihood of modification of urinary steroid excretion pattern by renal metabolic processes is quite likely, one must presume that urinary excretion patterns do not necessarily represent the steroid patterns existing in the circulating body fluids. Study of the steroid patterns of body fluids (blood) will eventually have to tell us the story. Very few chemical problems are more complex, individualized, or important than the steroid pattern. To what extent more satisfactory study of this subject will enlighten us so far as cancer is concerned is conjectural, but it seems highly promising.

### EXTENSION OF LIFE EXPECTANCY

In the joint study participated in by Alyea, Cahill, Campbell, Colby, Henline, Jewett, McClelland, Nesbit, O'Conor, Prather, Scott, Shaw, Smith, and Toulson,[9] it is concluded among other things that "the maximum benefit is best achieved by the institution of treatment as soon as diagnosis is established." My experience does not confirm this statement. The first seven patients I treated lived an average of 37½ months. In all the disease was advanced and immediate relief was needed. I would estimate that these patients with such severe conditions had an expectancy extension of not less than two years, as compared with what it would have been without treatment. In instances in which pain is not a factor and the trend is generally favorable, I do not castrate or give estrogens. At the present time I have a number of patients who have not had castration or estrogens and whose general course is satisfactory. I cannot see how the immediate institution of treatment could affect the expectancy as favorably as the withholding of therapy until unfavorable trends demand it. Now, as to public statements for general lay consumption so far as expectancy is concerned: Recently a newspaper column stated that endocrine treatment of prostatic cancer was not a cure. To be sure, no one has proved it a cure, but, on the other hand, we now have patients with absence of local and general metastases for as long as 10 or more years who are still alive. In 1905, Lett reported 1 of 99 castration cases of breast carcinoma as a possible cure. It is unjustifiably demoralizing to state that treatment cannot result in a cure.

9. Nesbit, R. M., and others: Endocrine Control of Prostatic Carcinoma: Clinical and Statistical Study of 1818 Cases, J. A. M. A. **243**:1317-1320, 1950.

### COMPLICATIONS INCIDENT TO CASTRATION OR ADMINISTRATION OF ESTROGENS

1. Vasomotor instability following castration. Patients with this condition are best treated, but not always satisfactorily, by the administration of barbiturates, bromides, *d*-amphetamine sulfate (dexedrine®), or estrogens. 2. Punctate ecchymotic phenomena (following estrogen administration). These respond to the administration of calcium gluconate either orally or intravenously. 3. Thrombophlebitis or pulmonary infarct. The patients respond to the administration of calcium or the withdrawal of the estrogen or both. 4. Cerebral hemorrhage. Cerebral hemorrhage, which in my opinion is a definite hazard, should result in the withdrawal of estrogen administration, and the administration of calcium should be instituted.

Recently progesterone has been injected directly into the arterial tree in animals. This approach to estrogen therapy in humans will have to be appraised as time goes on.[10]

Localization of osseous metastases by means of Geiger counters following the intravenous injection of gallium isotopes demonstrates osseus metastases before roentgen evidence is present. The injection of gallium isotopes relieves osseous metastatic pain in some instances and is definitely contributory in the field of pain relief. This work was begun by W. C. Mulry [11] and is being continued by King at the National Naval Medical Center at Bethesda, Md.

The administration of nitrogen mustard has been beneficial in some patients who have not responded to the castration-estrogen regimen. At this time it would seem appropriate to state that there is no such thing as a specific substance to be used for a specific type of cancer. It is not infrequent to observe satisfactory response to types of treatment when they are tried on a trial and failure basis in the treatment of a malignant process.

### CONCLUSIONS

The steroid chemical treatment of prostatic cancer has been a brilliant contribution in the field of chemical cancer control. Much more remains to be done in the various chemical fields and especially in the field of steroid pattern study.

Nitrogen mustard may be found effective in some instances.

There is justification for administering chemical compounds used in other fields in the therapy of cancer if the patient and the physician wish to try them.

Castration or the administration of steroids should not be instituted until definite indications develop.

1801 I Street N. W.

### ABSTRACT OF DISCUSSION

DR. EDWARD N. COOK, Rochester, Minn.: These two papers, I think, are worthy of comment; the authors should be commended for keeping before our minds this problem of chemistry as related to malignancy.

As Dr. Huggins fostered it, years ago, and is continuing to work on it, I think it cannot help but be one of the most hopeful signs that, before too many years go by, we shall undoubtedly come upon a much better understanding of the whole problem of malignancy, by chemical methods.

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10. Cromer, K.: Personal communication to the author.

11. Mulry, W. C., and Dudley, H. C.: Studies of Radio Gallium as a Diagnostic Agent in Bone Tumors, J. Lab. & Clin. Med. **37**:239-252, 1951.

I wonder whether all of you appreciate what a terrific problem is involved in attempting to evaluate any method of therapy in relation to prostatic carcinoma.

In the early days, Broders and Bumpus reported a five year survival of patients for whom a diagnosis of carcinoma of the prostate was made without any form of therapy whatsoever. When you have such a report to start with, it is a pretty difficult problem to say this, that, or anything else is doing such wonders.

I have been of the mind to give diethylstilbestrol to most of my patients shortly after I have made the diagnosis. I am very much interested in Dr. Herbst's comment that he does not believe it should be given at that time. I am not so sure he is not right.

Of interest is the exhibit of Dr. Flocks, in the auditorium hall, in which he has shown us that in those patients to whom diethylstilbestrol was administered for, perhaps, two years there was some change in the comfort and, perhaps, the survival rate, but at the end of five years he did not see a great deal of difference in the survival rate as compared with that of the group of patients to whom no estrogens were given or no orchidectomies performed.

I cannot help saying that I believe it will be a period of years, perhaps 10 or 15, before we can very satisfactorily evaluate the efficacy of diethylstilbestrol-estrogen administration, or the efficacy of orchidectomy, in treatment of carcinoma of the prostate, because there is such a great difference in the length of time these patients can live without any particular therapy.

Certainly we are all thoroughly familiar with the comfort we can give patients with diethylstilbestrol or orchidectomy when pain and general malaise have developed. I think we should continue to give them this relief, but I implore all of us to evaluate most carefully the results obtained, because it is very easy to be confused by them.

I was interested in Dr. Herbst's remarks concerning the sedimentation rate. I would agree with these statements. It has seemed to me that, while it is not always absolutely true, nevertheless a rising sedimentation rate to me has been a sign of extension of the disease and, probably, the approach of a terminal phase.

Dr. William A. Milner, Albany, N. Y.: I am afraid I have not been a very good choice to discuss Dr. Herbst's paper. To be a good discussant, one should differ in his opinions from the author, but I am afraid I will have to admit I am quite in accord with most of what Dr. Herbst has presented.

I am a firm believer in transurethral operations for all carcinomas of the prostate, with the exception of those which present reasonable chance for cure by radical operation.

If the patient when first seen was not amenable to radical operation, I doubt very much if he should be later treated this way after hormonal therapy; I see very little to gain and much to lose.

I agree with the author that merely the diagnosis of cancer of the prostate should not call for the removal of two of the patient's most prized possessions.

For example, I have one patient whose diagnosis was cancer, without question, and who is living and well without clinical or physical signs of cancer eight years following the time the diagnosis was made before transurethral prostatectomy. He has had no estrogens and was not castrated. Many patients will go for months or years without signs of disease, in spite of no estrogenic therapy.

Orchiectomy is the treatment of choice if hormonal therapy is to be considered. If some quick, inexpensive laboratory test can be made to tell us when sufficient estrogen is being given, then, and only then, can estrogenic therapy be employed very intelligently

I feel very strongly that the patient should know the nature of his disease. I think we should always be optimistic to him about it, but, in my experience, the patient who knows why he should do, and possibly expect, certain things is always an easier and a happier patient to care for. I sincerely believe that when we begin to consider the administration of estrogens for control of symptoms is the time to do the orchiectomy.

There is very little real difference between estrogenic and radiologic castration and surgical castration, except that I believe the results will be better after the surgical type.

Hamilton has shown that the sedimentation rate usually rises to rather unusual levels after orchiectomy. This is associated with a decrease as high as 10% in the hemoglobin of the average patient, with changes in the red corpuscles themselves.

The report of Flocks on the use of cortisone on a limited number of patients is extremely interesting. Although he could not note actual change in the disease, he reports that all patients felt improved.

The only patient I have had experience with, so far as cortisone treatment is concerned, has gone downhill after orchiectomy. His diagnosis was first made in 1946, as a result of a chest roentgenogram which showed metastasis. This diagnosis was later confirmed by a transurethral resection and orchiectomy, in 1949. In January, 1950, he weighed 92 lb. (42 kg.), was in bed constantly, and required a good deal of opiates for pain.

He was given 100 mg. of cortisone every other day. His weight has now risen to 128 lb. (58 kg.) and he does a little work in his shop. He needs opiates occasionally but has shown rather remarkable improvement. There has been no evidence by roentgenogram of regression of the metastasis.

One of the most reliable prognostic signs that I know of is the actual microscopic picture of the prostate removed at operation. During the last 10 years it has been my privilege to see between 500 and 600 patients with prostatic cancer who were treated surgically, and it seems almost invariable that those patients who have the typical glandular type of tumor, with marked tendency to form plastids, are the patients who respond best after gastrectomy. This group includes approximately 85% of all patients. The other 15% is made up of those patients in whom the tumor is highly antiplastic and shows absolutely no tendency of gland formation and in which the cells seem to grow wildly in all directions in large sheets and masses of cells. These are the patients who seem to derive little or no benefit from any type of therapy and who usually die within 12 months or less.

DR. HERBST, Washington, D. C.: Before I close my discussion, I should just like to say a word about Dr. Shivers' paper, so far as using estrogen and other types of therapy on cancers is concerned.

His case was a spectacular one, and we do not understand it. However, on that basis I think that we are justified in using some of these treatments which are not too complicated to institute, even though our rationale for such therapy is not too clear.

I have seen castration spectacularly improve the status of a case, even with most extensive nonmelanotic melanosarcoma. There does not seem to be any apparent correlation here but it has been an observed phenomenon. If we consider the chemical composition of the human body, we know that in giving excessive doses of estrogen to the male and tremendous doses of androgens to the female the chemical soil of the person will be upset to some extent. In general, results have demonstrated that these effects seem to be beneficial so far as the course of the cancerous growth is concerned. Hormone therapy is used not only in the genitourinary tract but in other fields as well.

I should like to reiterate a statement I made previously in my remarks; namely, that there is no question about the advisability of instituting surgery whenever it is possible to remove the prostate gland. Today, however, the extent of surgery in prostatic disease actually depends on the opinion of the individual surgeon who is confronted with the responsibility of handling the case. He must decide whether removing the prostatic mass and the adjoining tissue is going to be a reasonable thing, so far as the extension of the life-expectancy of the patient is concerned.

# Case Reports

## RECURRENT MYXOMATOUS CYST OF THE SKIN

ALEXANDER E. PEARCE, M.D.
RUSSELL W. WELLER, M.D.
AND
NATHAN STEINBERG, M.D.
PHILADELPHIA

MYXOMATOUS lesions are generally accepted as being either true neoplasms or foci of mucinous degeneration. Those involving the skin are localized in a zone of dermis or subcutaneous tissue, and they usually present cystic centers with no definite cellular lining. The wall, which is indefinite in outline and is made up of collagen fibers, usually sends thin, irregular trabeculae toward the center of the cyst, producing a lace-like pattern in which mucoid material is seen. The material is probably hyaluronic acid. Although the lesions are innocuous in appearance, both grossly and microscopically, recurrence may take place repeatedly, even after complete excision of the affected area. Malignant transformation, however, has not been reported. Recurrence of the lesion usually follows excision, drainage, curettage, carbon-dioxide-snow treatment, or cauterization, but Jacox and Freedman [1] noted that the tumors completely disappeared after low voltage roentgen therapy of 1,500 to 1,600 r. Patients who have pricked open cysts of this type, which were superficial, report prompt recurrence of the lesion in two to four weeks.

Gross [2] in 1937, reviewed the literature and tabulated 14 authentically reported cases of myxomatous cysts of the skin and added 7 cases of his own. Jacox and Freedman [1] reported seven cases, comparable to those of Gross, occurring most frequently in the fourth to the sixth decade, the youngest patient being 26 years of age. The average age for the occurrence of these cysts was 48 years. All patients were white, and 75% were women. The lesions had been noted by the patients for several months. One lesion was present on a toe and the others on the fingers, most commonly the dorsal aspect of the distal interphalangeal joint and usually on one side of the midline. The lesions usually were painless, both single and multiple, and usually measured from 0.3 to 1.2 cm. in diameter. They appeared as small nodules which sometimes were translucent if in close proximity to the epidermis. Since they usually arose in the dermis, the skin could not be moved over them. Stout,[3] in a general review of myxomas, cited 18 cases of myxomatous lesions of the skin from the literature and added 4 of his own cases. Myxosarcomas of the skin

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1. Jacox, H. W., and Freedman, L. J.: Roentgen Treatment of Myxomatous Cutaneous Cysts, Radiology **36**:695 (June) 1941.

2. Gross, R. E.: Recurring Myxomatous Cutaneous Cysts of Fingers and Toes, Surg., Gynec. & Obst. **65**:289 (Sept.) 1937.

3. Stout, A. P.: Myxoma, Tumor of Primitive Mesenchyme, Ann. Surg. **127**:706 (April) 1948.

have been reported by Maynard [4] and Kusnetz.[5] It is interesting to note, as in Maynard's [4] report, that myxosarcomas sometimes arise in scleroderma lesions. Bianco [6] reported a large pedunculated rapidly-developing myxoma of the vulva.

Myxomas have been more commonly reported in the heart, the mandible or maxilla, but rarely in long bones, zygomatic bone,[7] or alveolar process.[8] The osseous lesions usually present areas of cystic degeneration, often with hemorrhage. Stout [3] reported the case of a 2-year-old child with a myxoma of the right maxillary sinus.

The following case is reported because of the rarity of the lesion, particularly because of the previously unreported location of the lesion, and the age of the patient. The principal reason, however, for drawing attention to this lesion is its unusual ability to recur.

## REPORT OF A CASE

An 8-year-old white girl was admitted to Hahnemann Hospital, Aug. 21, 1951, with the complaint of a mass at the base of the first metacarpal of the right wrist. This mass was first noticed two years before by the child's mother. Similar masses had been excised three times during the previous two years, with recurrence within one to eight months following each procedure. Although no pathologic examination was performed after any of these operative procedures, the physicians who excised the lesions reported that grossly each consisted of a small cystic focus in the dermis containing mucinous material.

Physcial examination revealed a rounded translucent nodule 0.8 cm. in diameter on the dorsal-lateral aspect of the first metacarpal bone of the right wrist (Fig. 1). The mass was well circumscribed and immobile. With the area under local anesthesia, this nodule along with a wide area of normal skin and subcutaneous tissue was excised. Six days later, when the sutures were removed, and three weeks later, in a follow-up visit, it was noted that the wound had healed and there was no evidence of recurrence. Sixty-two days after the original resection, the patient returned with the complaint of a nodule beneath the scar of the recent surgical excision. The nodule was approximately the same size as noted previously but appeared to be deeper within the subcutaneous tissue. The patient stated that she had noticed this nodule for the first time two weeks before admission. On Oct. 22, the lesion was excised along with wide margins of normal skin and subcutaneous tissue. A split-thickness skin graft was then taken from the left thigh and applied to the defect. The patient was discharged three days later with a complete take of the graft, and there was no evidence of recurrence on May 5, 1952.

*Pathological Description.*—Examination of the specimen removed at the first operation at Hahnemann Hospital revealed an elliptical piece of white skin and subcutaneous tissue measuring 1.2 by 2.8 by 0.8 cm. On the surface was a well-healed linear scar, and approximately in its center was a superficial thin-walled cyst, 0.7 cm. in diameter. Cut section revealed a well-circumscribed cyst filled with colorless, mucinous material. The contents and wall of the cyst blended indefinitely into the surrounding tissue in some areas. Surrounding the lesion there was a margin of uninvolved skin, 2.1 cm. on two sides and 0.5 cm. on the other two cutaneous sides, and 0.2 cm. of subcutaneous tissue. Microscopic examination of this lesion revealed a fairly well-circumscribed, partially cystic lesion extending from the papillary layer of the dermis, just

4. Maynard, M. T. R.: Myxosarcoma of Skin: Report of Case, California & West. Med. **57**:142 (Aug.) 1942.

5. Kusnetz, M. M.: Myxosarcoma of Skin, Urol. & Cutan. Rev. **38**:873 (Dec.) 1934.

6. Bianco, A. A.: Myxoma gigante da vulva, An. brasil. ginec. **24**:345 (Nov.) 1947.

7. Ackerman, L. V., and Stout, A. P.: Myxoma of Zygomatic Bone, J. Missouri M. A. **46**:279 (April) 1949.

8. Lopez, M.: Myxomatous Tumor of the Alveolar Process with Typical Evolution but with Good Progress, Clin. Odont. **3**:58-60, (March) 1948.

9 and 10. Footnotes deleted.

Fig. 1.—Artist's sketch of lesion on wrist showing location in old surgical scar (first admission).

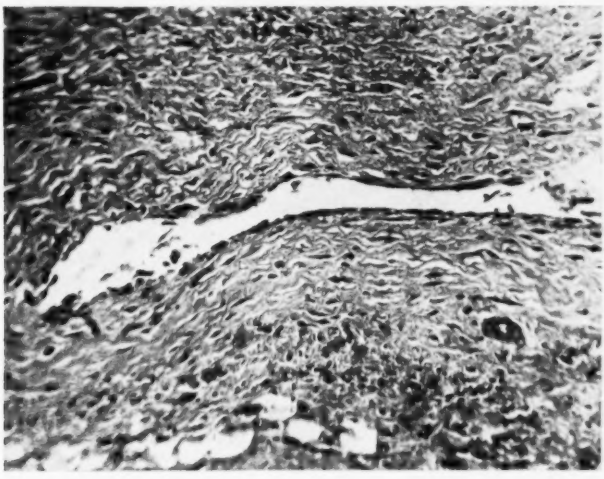

Fig. 2.—Ramification of wall of cyst showing plump, oval, hyperchromatic nuclei in collagenous stroma; × 100 (second admission).

beneath the basal layer of the epidermis, into the superficial layers of the subcutaneous tissue. The center of the lesion was made up of widely separated, plump, oval nuclei with thin, bipolar, cytoplasmic processes which fused with those of surrounding cells. Between these processes there was pale-blue, homogenous material in small amounts. In some parts of the margin of this cystic lesion, similar plump cells, which were widely separated by lace-like spaces in which mucin was present, extended independently and indefinitely into the surrounding connective tissue. Serial sections revealed no evidence of incomplete removal of any portion of the myxomatous tissue and no evidence of origin from nerve sheaths or other specific tissue. Because the tissue had been fixed in neutral formalin, stains for mucin were not conclusive.

Gross examination of the second surgical specimen revealed an elliptical piece of white skin and subcutaneous tissue measuring 2.4 by 4.0 by 1.0 cm. On the surface was a well-healed linear scar. Cut section revealed a cyst deep in subcutaneous tissue, beneath the scar, measuring 0.7 cm.

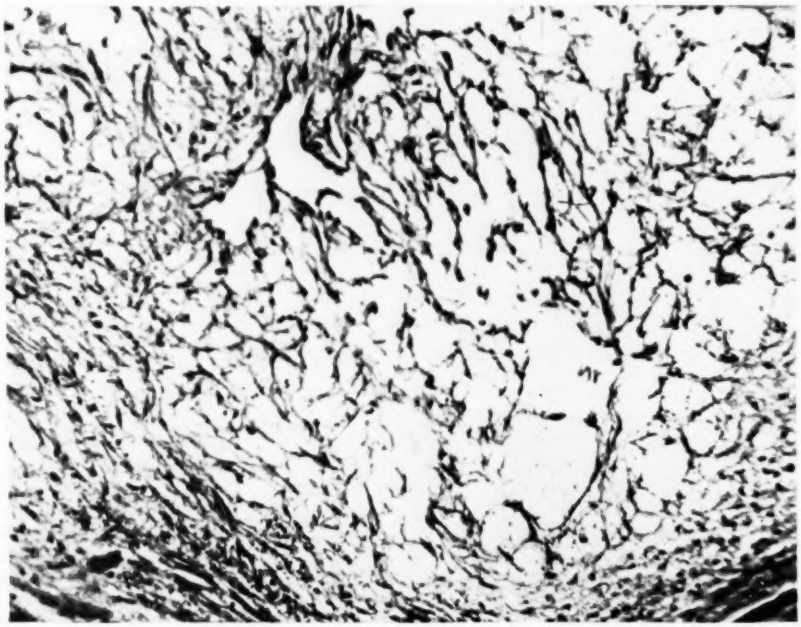

Fig. 3.—Focus of myxomatous degeneration near wall of cyst; × 100.

in diameter. Except for its location, the cyst appeared similar grossly to the preceding lesion. Microscopically in the dermis and subcutaneous tissue many foreign body granulomas containing suture material were seen. The cyst seen grossly was indefinitely lined by a thin layer of cells resembling fibroblasts (Fig. 2), and just beyond the wall in the subcutaneous fibrous tissue was a focus of lace-like myxomatous tissue similar to that described in the preceding specimen (Fig. 3). Again no evidence of incomplete removal was noted after multiple sections were examined.

## COMMENT

The preceding gross and microscopic characteristics were basically similar to those described by other authors. Gross [2] has, in addition outlined his interpretation of the pathogenesis of these lesions. He stated that the first variation from normal is focal degeneration of collagen of the dermis. A few fibroblasts remain and between them is a faintly basophilic staining material which gradually increases,

forming a cyst with an irregular wall. If left undisturbed the inner wall becomes rounded, dense, and well-defined, with surrounding normal-appearing dermis. There is no appreciable leucocytic infiltration.

The origin of these cystic lesions is unknown. Theoretically the following factors have been considered: (1) repeated trauma (because of location and occupation in many of the reported cases which necessitated considerable use of the hands) causing direct injury or thrombosis of small blood vessels, (2) degeneration of connective-tissue tumors, (3) variant of Heberden's nodes, (4) herniation of synovial membranes, and (5) viral infection, as in some myxomatous lesions in rabbits.

It is interesting to note the statement made by Gross [2] concerning ganglia, in which he suggests that a difference in origin of ganglia from outpocketings of joint or tendon sheath cavities or from degeneration of connective tissue may account for the 30% recurrence following surgical removal. Willis [11] states that most of the myxomatous lesions he has examined showed structural evidence of nerve sheath origin or suggested the likelihood of such origin. The case presented here, as well as the cases reviewed, did not substantiate this statement.

The differential diagnosis of these lesions rests between ganglia, synovial cysts, Heberden's nodes, fibroma or neurofibroma with myxomatous degeneration, circumscribed myxedema, and focal lesions of viral etiology.

## SUMMARY AND CONCLUSIONS

A recurring myxomatous cyst of the wrist of an 8-year-old girl is reported. In the 28 cases previously reported we are unable to find an example of a myxomatous cyst in the above location or occurring in a person younger than 26 years of age. Although these lesions are innocuous in appearance, the preceding case report adds to the literature another example of the ability of these cysts to recur repeatedly after surgical excision. We cannot fully agree with Gross [2] that these lesions are characteristic of degeneration and are not neoplastic. Mildly caustic low-voltage roentgen therapy is apparently curative.

230 N. Broad St.

11. Willis, R. A.: Pathology of Tumors, St. Louis, C. V. Mosby Company, 1948.

# CLINICAL SIGNIFICANCE OF HETEROTOPIC PANCREAS IN WALL OF STOMACH

## Report of a Case and Review of the Literature

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MILWAUKEE

NO MATTER how rare a medical entity may be, if it has the potentiality of producing any serious consequence, it certainly is worthy of consideration. Since Klob [1] first called attention to the aberrant pancreas, in 1859, there have been 548 cases of heterotopic pancreatic tissue reported in the literature.

There are numerous contributions as to the origin of this tissue. The one most widely accepted is that of Moore [2] who suggests that different cases present different factors of possible origin: (1) that the heterotopic tissue develops from the primary anlage; (2) that inflammatory or embryonal adhesions cause subsequent detachments of a mass of pancreatic cells, and (3) that the cells of the secondary snared-off anlage of Warthin are still undifferentiated entoderm and are capable of differentiating into pancreatic acini, islands of Langerhans, ductal epithelium, and glands of Brunner.

Heterotopic pancreatic tissue has been noted in the stomach, gall bladder, spleen, mesentery, omentum, ileum, duodenum, jejunum, Meckel's diverticulum, liver, and cystic duct, the primary incidence being in the stomach, duodenum, and jejunum.

The histologic features found [3] are all similar to that of the pancreas itself, the commonest histologic location being in the submucosa alone.[3]

Pancreatic heterotopia may be the cause of several types of pathologic changes in the adjacent tissues: hemorrhage, diverticulum formation, inflammation, fat necrosis, and ulceration. The same pathologic changes which occur in the pancreas can occur in the heterotopic pancreatic tissue. Malignant changes are more likely to take place in the heterotopic pancreatic tissue than in the pancreas proper.

The syndromes presented by a pancreatic heterotopia are generally those of gastric or duodenal ulceration, cholecystic disease, or indeterminate digestive symptoms, but the findings do not fit clearly into any one of these diagnoses.

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Dr. James M. Sullivan made recommendations for the preparation of this paper.

From Mount Sinai Hospital, Department of General Surgery, and Marquette University School of Medicine, Department of Anatomy.

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2. Moore, R. A.: Accessory Pancreases: Report of a Case with a Discussion of Their Pathology and Origin, Am. J. Path. **5**:407-414, 1929.

3. Borbosa, J. J.; Dockerty, M. D., and Waugh, U. M.: Pancreatic Heterotopia, Surg., Gynec. & Obst. **82**:527-541, 1946.

Fig. 1.—Barium study of stomach, demonstrating constant filling defect on greater curvature.

Fig. 2.—Barium study of stomach, revealing space-occupying lesion in stomach.

In Borbosa's series of cases in which the heterotopic tissue was in a gastric location, the diagnosis of a benign tumor was made in 50%, of ulcer in 20%, and of malignant tumor in 20%. The mass was missed in 10%. In all the others, the roentgenological diagnosis of duodenal ulcer was made, although in only one was an ulcer actually present. The x-ray diagnosis of a gastric or duodenal polyp is the nearest that one can actually get to the precise and final diagnosis made by the pathologist. This was exemplified in our case (Figs. 1 and 2).

In view of the equivocal character of the x-ray findings and the strong clinical history, these alone may influence the surgeon to a considerable degree, even in the absence of a positive demonstration of an ulcer crater.

## SURGICAL TREATMENT

When the pancreatic heterotopia is located in the stomach or duodenum, simple local excision, when possible, is sufficient to bring about relief of symptoms. At times duodenal reconstruction, pyloroplasty, or subtotal gastric resection may have to be carried out. The operative procedure advised for pancreatic heterotopia in locations other than the stomach and duodenum is complete but simple extirpation; however, no generalizations can be made, for so varied are the locations. Whenever heterotopic pancreatic tissue is found in the stomach or duodenum during the course of an operation for some other surgical lesion, its excision is indicated to avert future trouble unless the risk of the procedure outweighs the advantages of a removal.

## REPORT OF A CASE

K. S., a 62-year-old white woman, was hospitalized because of upper abdominal pain, belching, bloating, nausea, and vomiting. Her dyspepsia was constant, more so, however, after meals. These symptoms had been present intermittently for two years and had been treated sporadically with a medical ulcer regimen which gave her temporary relief. The patient had lost no weight and stated that she had never had blood in her stool and had never manifested any jaundice.

The past medical history was noncontributory, and physical findings and laboratory studies revealed no significant abnormalities.

Roentgen studies of the colon and gall bladder showed essentially normal conditions. Barium studies of the stomach, esophagus, and duodenum were reported as follows: Examination showed normal passage of barium through the esophagus into the stomach. The stomach showed a normal mucosal pattern and normal peristaltic activity; however, there was noted a constant filling defect on the greater curvature, approximately 1½ to 2 in. (4 to 5 cm.) from the pylorus, measuring approximately 1.5 cm. in diameter. The mucosal folds presented a normal appearance. The duodenal bulb filled well and showed no defects or deformities. The diagnosis was polypoid tumor of the stomach (Figs. 1 and 2). In view of the roentgenological findings, the patient was scheduled for surgery, and a subtotal gastrectomy with an anterior gastrojejunostomy was done. The patient had an uneventful postoperative course and was dismissed on the 10th postoperative day.

*Pathologic Report.*—Gross Examination: The specimen was the distal two-thirds of a stomach. The greater curvature measured about 14 cm. and the lesser 7.5 cm. The pyloric ring and about 3.5 cm. of the first portion of the duodenum were included. The mucosa of the latter was congested. The mucosa of the stomach proper showed a mound-like elevation (Fig. 3) covered by mucosa, which at the apex of the mound dipped down into a centrally located pit (pseudodiverticulum). In the serosal surface (Figs. 4 and 5) two oval-shaped bulging nodules were noted. One was located on the greater curvature right across the pyloric ring, partly extending into the

Fig. 3.—Gross specimen as it appeared after fixation, demonstrating mound-like elevation covered by mucosa, which at apex of mound dips down into a centrally located pit. Note pseudo-diverticulum proximal to pyloric ring.

Fig. 4.—Showing serosal surface of stomach on which oval-shaped bulging nodules consisting of heterotopic pancreatic tissue are seen.

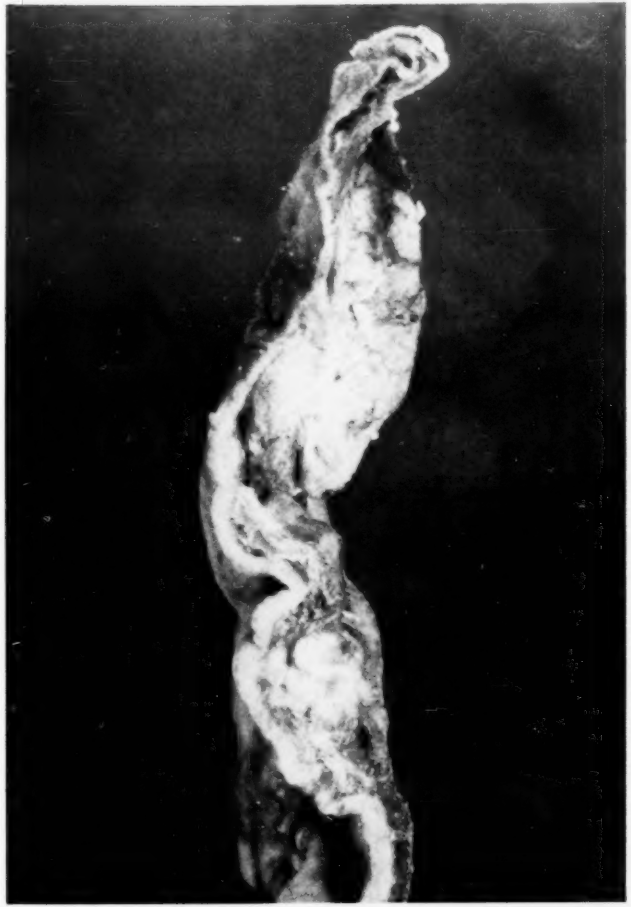

Fig. 5.—Longitudinal cross section through gross section of stomach and duodenum, demonstrating heterotopic pancreatic tissue in relation to mucosa and serosa.

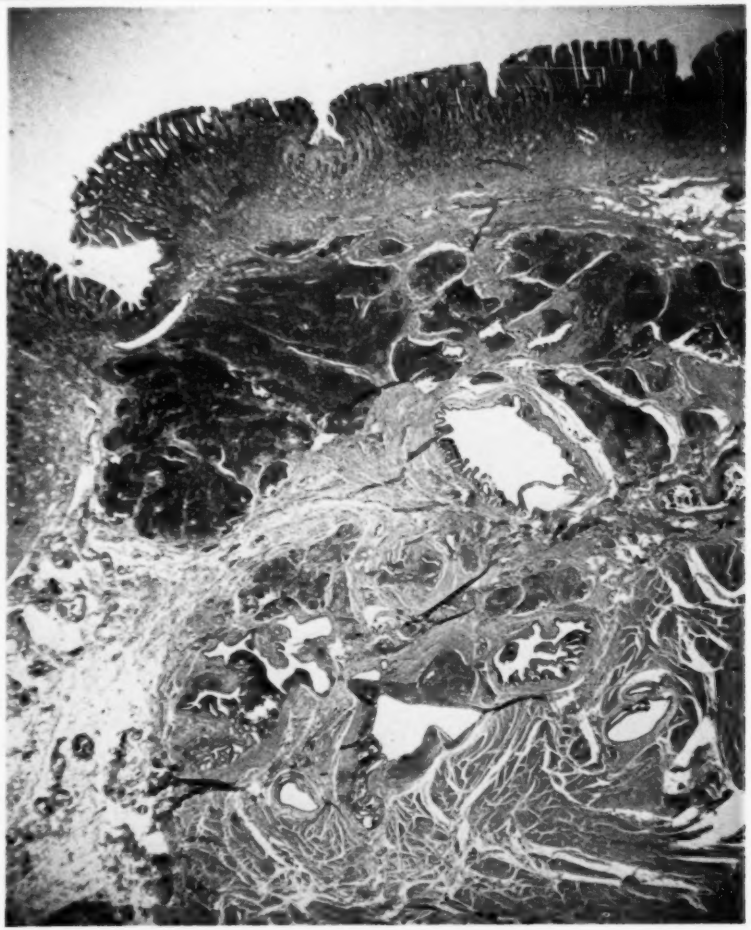

Fig. 6.—Photomicrograph illustrating relationship of heterotopic pancreatic tissue to the muscularis mucosae of stomach.

duodenum and partly into the magenstrasse. This nodule measured 3 by 2 cm. On the surface it had a yellow color and on the cut surface a yellow-brown tint. Further examination of the cut surface revealed the presence of a lobulated gray-brown tissue. One and five-tenths centimeters proximal to this elevation there was a second, small similar lesion measuring 2 by 1.5 cm., which likewise was occupied on the cut surface by the same type of tissue as described above. Both lesions failed to involve mucosa. However, the mound-like projection of mucosa, as described above, was overlying the second nodule described (Figs. 3, 4, and 5).

Microscopic Examination (Figs. 6 and 7): Sections from the two nodules showed about the same features. The mucosal layers of the stomach and the first portion of the duodenum were essentially normal. Originating within the submucosa and extending in most areas through the muscle into the serosal coat was a considerable amount of pancreatic parenchyma. The latter

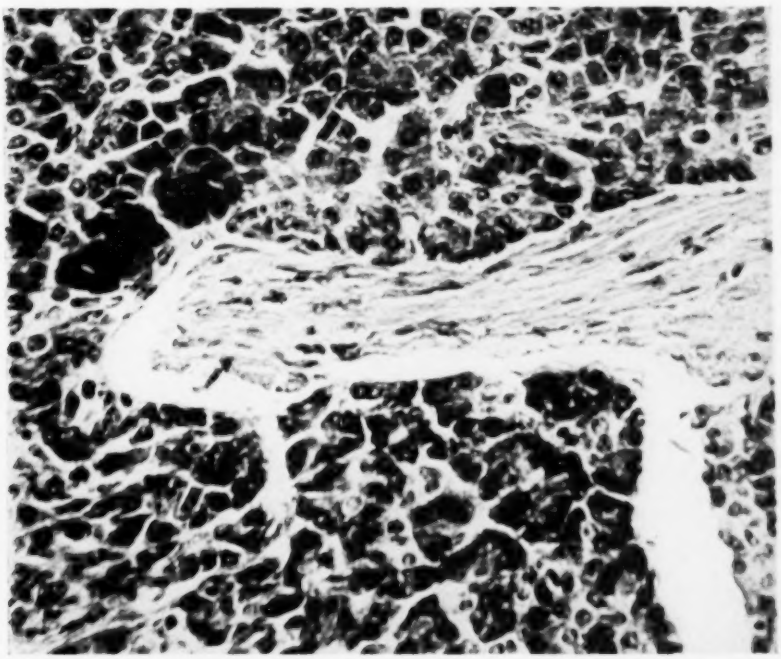

Fig. 7.—High power photomicrograph (× 700) of heterotopic tissue, demonstrating pancreatic alveoli and pancreatic ducts.

showed well-lobulated pancreatic alveoli and scattered numerous islets of Langerhans. In addition, there were variously shaped cross sections of pancreatic ducts. All structures were lined with a perfectly regular epithelium. There was a moderate degree of congestion of the submucosal zone, but any inflammatory reaction, so to speak, was absent. A diagnosis of accessory pancreatic tissue was made.

## SUMMARY

Another case of heterotopic pancreatic tissue in the stomach (located at two sites) has been presented. The patient manifested a clinical picture of indeterminate digestive symptoms which on investigation revealed the commonest misinterpreted

roentgenological finding of pancreatic heterotopia—namely, a polyp present in the prepyloric area of the stomach.

This patient also presented a peculiar and diagnostic alteration of the gastric mucosa, consisting of a mound-like projection, or as Benner [4] records it, a "pseudodiverticulum" overlying the aberrant tissue. We believe that if the gross characteristics are kept in mind, it will be of aid to the surgeon in the recognition of heterotopic pancreas involving the stomach.

212 W. Wisconsin Ave.

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# RECURRENT GALLSTONE SMALL BOWEL OBSTRUCTION

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COMPLETE small bowel obstruction due to gallstones is thought to be a comparatively uncommon surgical entity.[1] Consequently, such cases have not been stressed in medical teaching. Since the literature indicates that 1.7 to 6.2% of all complete small bowel obstructions are due to gallstones,[2] this situation seems paradoxical. During the past 5 years (1946-1951) there have been 217 cases of complete small bowel obstruction at the Buffalo General Hospital. Of the total number, eight cases have been due to gallstones. This represents a figure of 3.6% and is in accord with the literature.

In contrast to simple gallstone obstruction, cases of recurrence due to a second stone contained within the gall bladder at the time of initial surgery are rare.[3] We have been able to locate only five such cases [4] and wish to add the case herein described.

## REPORT OF A CASE

Mrs. A. T., aged 67, was admitted to the Buffalo General Hospital on Feb. 27, 1951, complaining of severe abdominal pain and vomiting. The past history revealed an episode of severe right upper quadrant pain seven months previously.

The patient appeared acutely ill. The temperature was 99.6 F. rectally; the pulse rate, 130; the respiration rate, 26, and the blood pressure, 120/80. The abdomen was moderately distended, with slight upper quadrant tenderness. No masses could be palpated.

A roentgenogram of the abdomen taken on admission gave the appearance of a complete small bowel obstruction. An oval, opaque density was present in the gall-bladder area, and the biliary radicals were gas-filled (Fig. 1).

Laboratory studies were noncontributory.

A diagnosis of complete small bowel obstruction due to gallstone was made, and the patient was prepared for immediate surgery.

At operation a gallstone measuring 4.2 by 3 cm. was found approximately 24 in. (60 cm.) from the ileocecal valve, completely obstructing the ileum. The stone was removed by ileotomy. No additional stones were present in the intestinal tract; however, the patient's condition would not permit exploration of the biliary area.

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Attending Surgeon (Dr. Milch); Assistant Resident Surgeon (Dr. Mendez), and Assistant Attending Physician (Dr. Murphy), Buffalo General Hospital.

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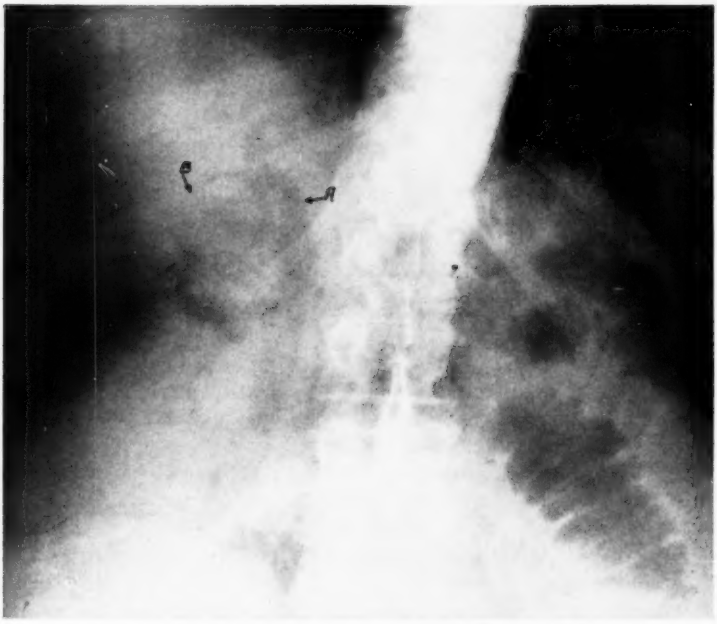

Fig. 1.—Roentgenogram of abdomen taken at time of patient's first admission to hospital. Note gas-filled biliary apparatus (*A*) and large opaque density (*B*) in area of gall bladder. Intestinal dilatation is evident.

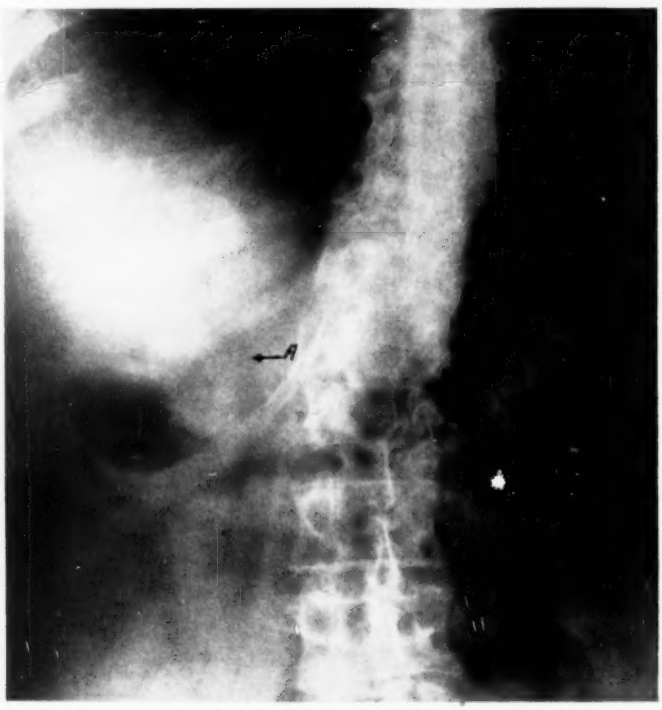

Fig. 2.—Roentgenogram of abdomen taken at time of patient's second admission to hospital. Again note gas-filled biliary tract (*A*). Previous opaque density in this area now absent. Intestinal dilatation again evident.

The patient was discharged from the hospital on the 17th postoperative day.

Because a second gallstone was shown roentgenographically to be present in the gall bladder, the patient was urged to return to the hospital. In spite of persistent and constant urging, she refused additional study.

In May, 1951, the patient was readmitted to the Buffalo General Hospital with a clinical picture similar to her original illness. Roentgenograms of the abdomen failed to reveal the opaque density formerly described in the area of the gall bladder. However, a similar density was now present in the lower abdomen (Fig. 2).

At the time of operation a gallstone measuring 4 by 2.5 cm. was removed from its site, approximately 24 in. (60 cm.) proximal to the previous ileotomy.

At the time of the patient's discharge, on the 18th postoperative day, we experienced no difficulty in convincing her of the need for corrective biliary surgery.

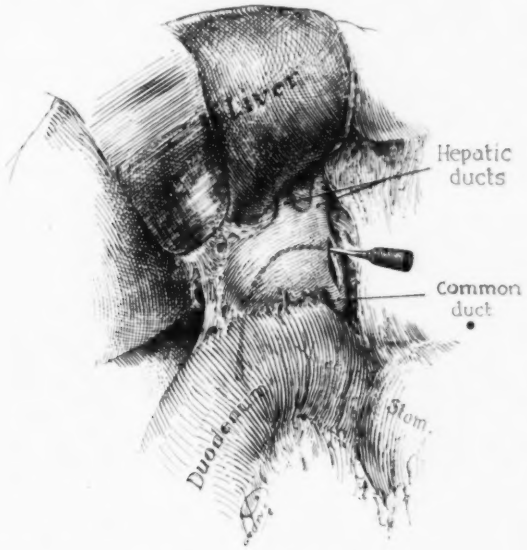


Fig. 3.—Illustrating pathologic anatomy present at time of exploration. Note that atrophic gall bladder actually forms a portion of wall of common hepatic duct and choledochus.

During August, 1951, the patient was operated upon for the third time. Visualization of the enterobiliary fistula was difficult. A communication was demonstrated connecting the gall bladder, right hepatic duct, and first portion of the duodenum (Fig. 3). The gall bladder was completely atrophic. No additional gallstones were found within the biliary apparatus.

The patient was again discharged to the care of her physician, on the 13th postoperative day.

## COMMENT

The diagnosis of small bowel obstruction due to gallstones is possible if one realizes that this condition is not rare. The patient who presents the clinical picture of small bowel obstruction with roentgenographic evidence of gas in the biliary radical must be suspected to have gallstone bowel obstruction.

In some instances roentgenographic demonstration of an opaque density within the dilated loops of small bowel is possible. Where no contraindications exist, the use of an oral contrast medium will often outline the enterocholecystic fistula.

It seems imperative to consider a gallstone as a likely cause of small bowel obstruction in elderly patients on whom no previous laparotomy has been performed.[5] This impression was valid in four of the cases seen at this institution.

Various authors indicate the mortality rate of gallstone intestinal obstruction to be about 60 to 70%.[6] The figure at this hospital for 1946 to 1951 was 12.5%, or one death in eight such cases. While we take some pride in this figure, we feel that the low mortality rate is a definite indication of the alertness of our radiology department.

After recovery from the acute obstructive episode, management of the fistula becomes the major problem. It is our opinion that surgical correction of the fistula should be undertaken as soon as feasible. Delay may invite additional hazards and complications. Unfortunately, the number of cases of recurrent gallstone intestinal obstruction are too few to support such a thesis adequately.

Most certainly, every case of gallstone obstruction should be restudied postoperatively in order to discern residual biliary pathology.

## SUMMARY

Small bowel obstruction due to gallstone in the intestine is not a rare surgical entity.

Cases of true recurrent intestinal obstruction due to a second gallstone not originally present in the intestinal tract are rare. We present the sixth such case available in the literature.

Roentgenographic signs suggesting the diagnosis are briefly discussed.

Early diagnosis and operation are imperative if the mortality rate is to be reduced.

We suggest the correction of existing biliary pathology as soon as feasible in order to prevent additional complications.

5. Downing, W. L.: Gall Stone Ileus: Report of 5 Cases, J. Iowa M. Soc. **38**:95, 1948.
6. Mast.[1] Holz.[4] Downing.[5]

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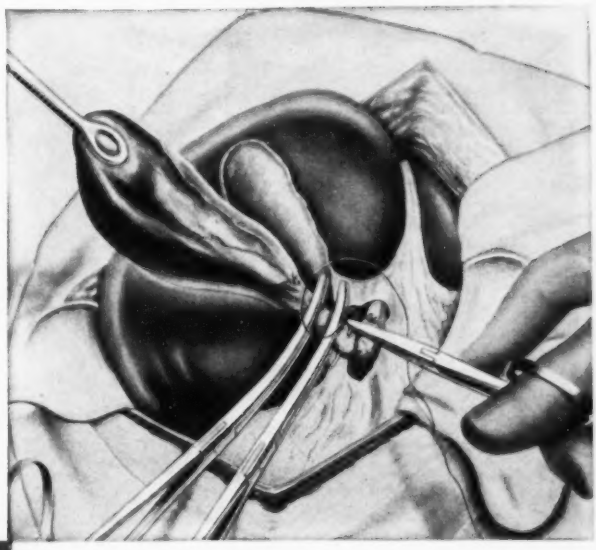

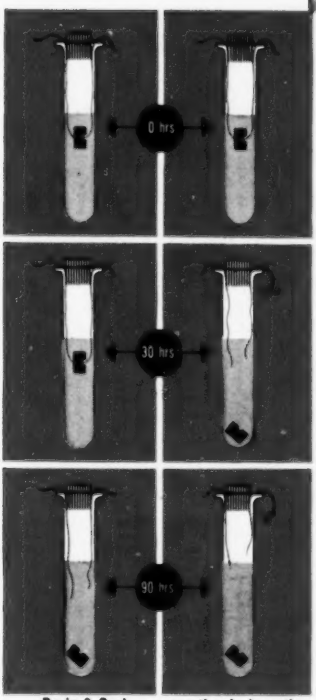


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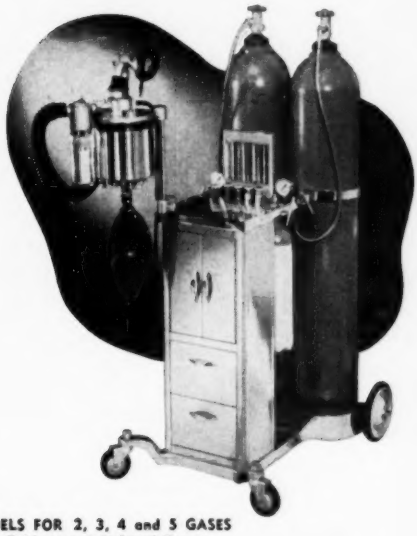

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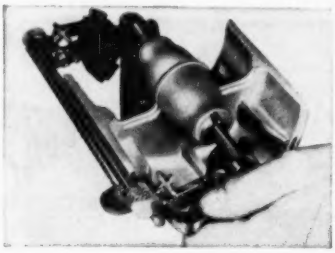

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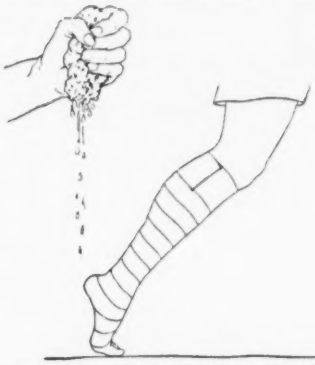

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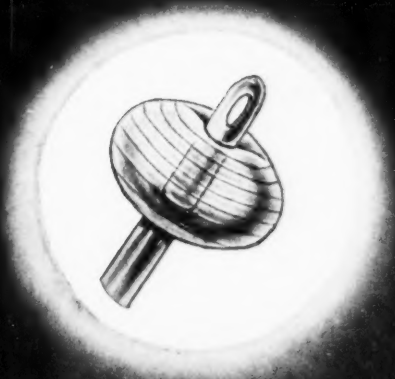

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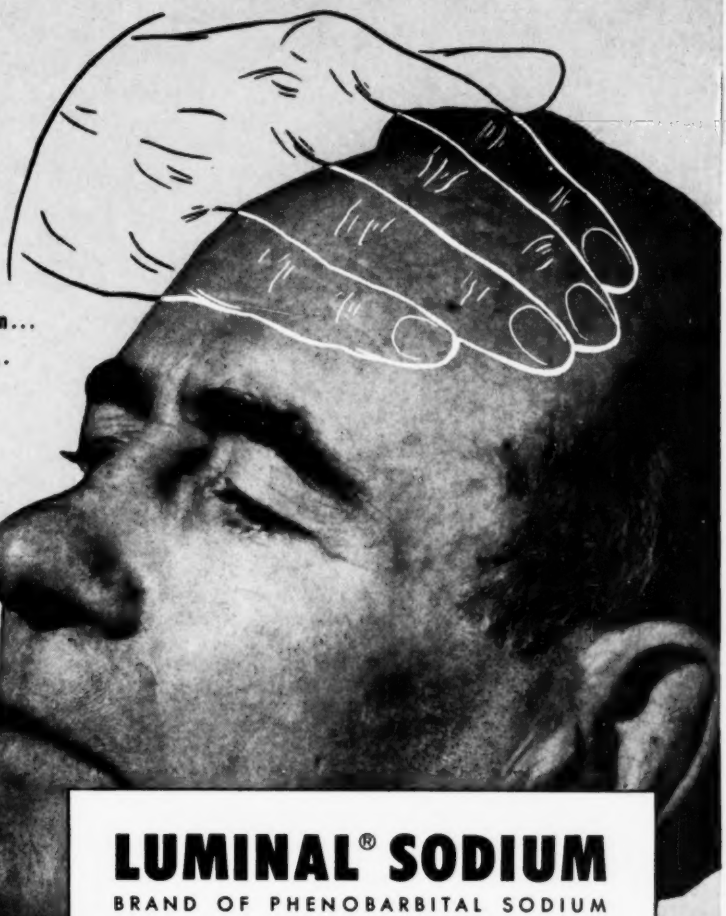

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